VISUAL EVOKED POTENTIALS IN DIABETES MELLITUS

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This dissertation entitled " VISUAL EVOKED POTENTIALS IN DIABETES MELLITUS" is submitted to the Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfillment of regulations for the award of M.D. Degree in Physiology in the examinations to be held during April 2012.

This dissertation is a record of fresh work done by the candidate **Dr. S.NAVURANG,** during the course of the study (2009-2012).

This work was carried out by the candidate herself under my supervision.

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The Ethics Committee, Coimbatore Medical College has decided to inform that your Dissertation is accepted / ~~Not accepted~~ and you are permitted / ~~Not Permitted~~ to proceed with the above Study.

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Date : 9/9/10

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Secretary
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CONTENTS

ABBREVIATIONS USED IN THE STUDY

- VEP VISUAL EVOKED POTENTIAL
- DM DIABETES MELLITUS
- IDDM INSULIN DEPENDENT DIABETES MELLITUS
- NIDDM NON INSULIN DEPENDENT DIABETES MELLITUS
- NPDR NON PROLIFERATIVE DIABETIC RETINOPATHY
- PDR PROLIFERATIVE DIABETIC RETINOPATHYS
- PR-VEP PATTERN REVERSAL VISUAL EVOKED POTENTIAL
- IFCN NATIONAL FEDERATION OF CLINICAL NEUROPHYSIOLOGY
- DCCT DIABETES CONTROL AND COMPLICATIONS TRAIL

VISUAL EVOKED POTENTIALS IN DIABETES MELLITUS

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ABSTRACT

BACKGROUND: Visual evoked potentials are electrical potential differences recorded from the scalp in response to visual stimuli. They are useful for investigating the physiology and the pathophysiology of the human visual system including visual pastways and visual cortex.They can be used effectively to study both normal and abnormal functions in the field of research. AIMS AND OBJECTIVES: To study the VEP responses in type 1, type 2 diabetic patients and controls. To compare the VEP responses in type 1 and type 2 diabetics. To assess the correlation between the duration of diabetes and wave patterns of VEP in type 1 and type 2 diabetics.To evaluate the association between the glycemic control and wave patterns of VEP in type 1 and type 2 diabetics.To compare the VEP responses in type 1 and type 2 diabetics in relation to glycemic control and duration of diabetes. MATERIALS AND METHODS: STUDY DESIGN: Combined cross sectional and case control study. This study was carried out in the Research laboratory of the Department of Physiology, Coimbatore medical college, Coimbatore. The study was approved by ethical committee.The study was carried out after explaining the procedure in detail and getting informed consent from the diabetic patients and normal subjects. A total of 80 subjects were included in the study of which 40 were diabetics (20 type 1 and 20 type 2) and 40 were controls.They were of 30 -70 yrs of age group.EXCLUSION CRITERIA: Diabetic patients with retinopathy, glaucoma, hypertension and cataract were excluded from the study.Pattern shift visual evoked potential test was performed in a specially equipped electrodiagnostic procedure room.The patients were seated comfortably one meter away pattern – shift screen. Subjects were placed in front of a black and white checker board pattern displayed on a video monitor. The electrodes were placed using conduction jelly after thoroughly cleaning the area. Recording electrode was placed at Oz, reference electrode was placed at Fz and ground electrode placed at M_1 position. Everytime,the pattern changes, patient's visual system generates an electrical response which was detected and recorded by surface electrodes. The patient was asked to focus his gaze on to the center of the screen. Each eye was tested separately. RESULTS: One way ANOVA and Student 't'test were used to asses the statistical significance. All data is expressed as mean ± SD. The mean value of P_{100} latency was significantly delayed in type 1and 2 diabetics as compared to controls (Pvalue :0.007 left eye,0.030 right eye). There was no statistically significant difference found between type 1 and 2 diabetics.The mean value of P_{100} latency was significantly prolonged in diabetics whose HbA1C is >7 % and with increased duration of diabetes. There was no statistically significant difference found between type 1 and 2 diabetics in relation to glycemic control and duration of disease . CONCLUSION: The delayed P_{100} latencies which were recorded in the absence of retinopathy are indicative of anterior visual pathway affection in diabetics. Therefore, VEP should be considered as a valid method for detecting prediabetic retinopathy, which could contribute greatly to the prevention of diabetic retinopathy and its complications.

KEYWORDS:

Visual evoked potential, Diabetes mellitus, Diabetic retinopathy.

Introduction

Diabetes mellitus is a heterogenous group of metabolic disorders characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. The majority of cases of diabetes fall in to two broad etiopathogenetic categories which are type 1 and type 2 diabetes.

Type 1 diabetes is the form of disease primarily due to beta cell destruction, which requires insulin for survival. It is characterized by the presence of auto antibodies like anti-islet cell or anti-insulin antibodies which reflects that beta cell destruction is due to autoimmune process. The rate of beta cell destruction is rapid in infants and children and slower in adults. They have low or undetectable levels of insulin and plasma C peptide [1].

Type 2 diabetes is the most common form of diabetes. It is characterized by disorders of insulin action or insulin secretion or both. Patients with type 2 diabetes

usually have insulin resistance rather than absolute insulin deficiency. This form of diabetes is associated with progressive beta cell failure and frequently goes undiagnosed for many years because the hyperglycemia develops gradually and in the earlier stages is not severe enough to produce the classic symptoms of diabetes. Both type 1 and type 2 patients are at increased risk of developing macrovascular and micro vascular complications. Macro vascular complications such as coronary artery disease, cerebro vascular accidents and peripheral vascular disease are not directly linked to the level of hyperglycemia but micro vascular complications like retinopathy, neuropathy and nephropathy due to micro angiopathy have been directly linked to glycemic control [2].

Type 1 diabetes is prominent as a disease of child hood, reaching a peak incidence around the time of puberty, but can present at any age.The highest rates of type1 diabetes in the world are seen in Finland and North European countries [3]. WHO in 1995 estimated that there 19.4 million people with type 1 diabetes and that the

number will rise to 57.2 million by 2025.

The development of type 2 diabetes are influenced by attained age. The Prevalence of type 2 diabetes increases as the age advances .

A study conducted in monozygotic and dizygotic twins show that more frequent concordance for diabetes among monozygotic than dizygotic twins, favours a greater role of genetic factors [1].

The world wide prevalence of diabetes has risen dramatically over the past two decades from an estimated 30 million cases in 1985 to 177 million in 2000. Based on current trends, more than 360 million individuals will have diabetes by year 2030.Although , the prevalence of both type 1 and type 2 diabetes is increasing worldwide, the prevalence of type 2 diabetes is rising much more rapidly because of increasing obesity and reduced activity levels as countries are becoming industrialized. Among microvascular complications, diabetics have 20-25 times greater risk of blindness as compared to the general population.

Diabetic retinopathy is well characterized by sight threatening chronic microvascular complication that eventually affects all patients with diabetes mellitus. Diabetic retinopathy refers to the retinal changes which is common after the disease has lasted approximately10 years. It usually occur in patients after the age of 20 years. It affects young or old according to their diabetic age and does not depend on the actual age of the patient. Duration of diabetes more than 10years, poor glycemic control, heredity, associated hypertension and pregnancy predisposes the occurence of diabetic retinopathy [4].

Electrophysiological tests play an important role in the examination of visual system and gives us information about the physiology of anatomical pathway with much less spatial or localizing information.Visual evoked potentials are evoked potentials in response to visual stimuli. In this technique, a visual stimulus is given to the subject and the net potential changes taking place in the visual cortex in response to stimulus are recorded from the surface electrodes placed over the scalp.

It is well acknowledged that VEPs are very useful for investigating the physiology and pathophysiology of the human visual system including visual pathways and visual cortex. They can be used effectively to study both normal and abnormal visual functions in the field of research.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

- To study the VEP responses in type 1, type 2 diabetic patients and controls.
- Comparing the VEP responses in type 1 and type 2 diabetic individuals.
- To assess the correlation between the duration of diabetes and wave patterns of VEP in type 1 and type 2 diabetics.
- To evaluate the association between the glycemic control of diabetes and wave forms of VEP in type 1 and type 2 diabetics.
- Comparing VEP responses in relation to glycemic control and duration of diabetes in type 1 and type 2 diabetes.

REVIEW OF LITERATURE

Diabetes is a disease known from ancient times. It is a condition that is extremely serious from both clinical and public health stand points. In 1674,Thomas willis, a physician and anatomist discovered that the urine of diabetic individuals was sweet. This was actually a rediscovery from an ancient Hindu document by "Sushruta" in India in about 4^{th} century BC who had described the diabetic syndrome as characterized by honeyed urine.

Later in 1776, England physician, Mathew Dobson demonstrated the excretion of sugar in urine in diabetics and he noted the residue of a crystalline material which had the appearance and taste of brown sugar.

In 1797, "John Rolto" a surgeon general of Royal artillery first applied the discovery of glycosuria to the quantitative metabolic study of diabetes.

Later in 1889, "Joseph Von Herring" and "Oscar Minkowski" discovered the role of pancreas in diabetes, which made a turning point in the history. "Sir Edward Albert Sharpey – Schafer" found that individuals with diabetes were deficient in single chemical produced by islets of Langerhans in pancreas and proposed the name "Insulin" from the Latin word "Insula" meaning "Island".

In 1921 , "Frederick Banting" and "Charle Best" demonstrated the first successful insulin preparation for the treatment of diabetes.

Diabetes is not a single disease entity but rather a group of metabolic disorders sharing a common underlying feature of hyperglycemia. Hyperglycemia in diabetes results from absolute insulin deficiency, impaired release of insulin by the pancreatic beta cells, inadequate or defective insulin post receptor regulation or the production of inactive insulin that is destroyed before it can carry out its action.

Diabetes may present with characteristic symptoms such as thirst, polyuria, blurring of vision, weight loss and polyphagia and in its most severe form with ketoacidosis or Non ketotic hyper osmolar coma which in the absence of effective treatment leads to stupor, coma and death .

CLASSIFICATION OF DIABETES [1]

*** Type 1 diabetes**

Beta cell destruction, usually leading to absolute insulin deficiency.

- Auto immune
- Idiopathic

*** Type 2 diabetes**

May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance.

*** Other specific types**

- Genetic defects of beta cell function
- Genetic defects in insulin action
- Diseases of the exocrine pancreas
- Endocrinopathies
- Drug or Chemical –induced
- Infections
- Gestational diabetes

Pathophysiology of type 1 diabetes

It is sub classified into type 1A and type 1B.

Type 1A is an autoimmune disease characterized by the pancreatic beta cell destruction and an absolute deficiency of insulin. These type of patients have anti glutamic acid decorboxylase (GAD) auto antibodies, islets cell antibodies (ICA) and decreased C-peptide level in their serum. In the presence of these auto antibodies, the patients can be diagnosed earlier before they progress to overt diabetes.

In type 1A, there is strong association with specific haplotypes or alleles at the DQ-A and DQ-B loci of the human leucocyte antigen.It is more likely to be associated with other autoimmune disorders such as Graves disease, Hashimoto's thyroiditis, Addison's disease, Coeliac disease, Vitiligo and Pernicious anemia. Viral infections such as Mumps, Congenital Rubella, Measles, Chicken pox, Coxackie virus and Echo virus in the new born are at high risk to develop autoimmunity.

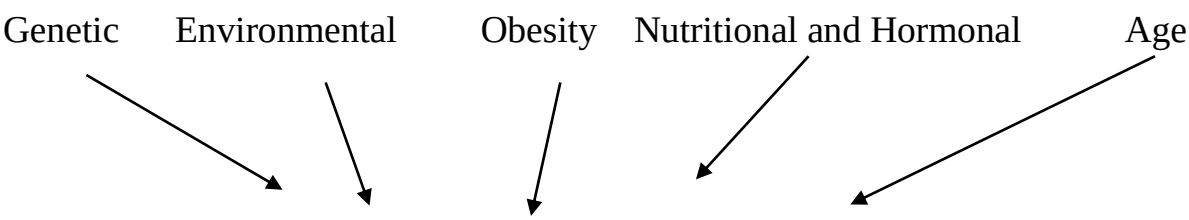
Type 1B (Idiopathic) diabetes is a form of diabetes with severe insulin deficiency without evidence of beta cell auto immunity. It is a more common form of diabetes in a childhood and it is characterized by the low insulin and C-peptide levels and

such patients are more prone to develop ketoacidosis [1].

Patho physiology of type 2 diabetes:

It is caused by a combination of peripheral resistance to insulin action and an inadequate secretory response by the pancreatic beta cells.

Insulin resistance develops from the complex interplay of genes, obesity, environmental, nutritional, hormonal factors and advancing age.



INSULIN RESISTANCE

Beta cell dysfunction :

The beta cell defect in type 2 diabetes is the loss of first phase (0-10 minutes after glucose intake) of glucose induced insulin secretion. This observation was first made in the late 1960s, when persons with type 2 diabetes

were noted to have a delayed insulin response to intravenous glucose, and later was recognized as loss of the first phase. The second phase is also impaired but to a lesser degree. There are many biochemical and molecular mechanisms have been proposed for the induction of beta cell dysfunction by hyperglycemia which includes excess glycogen storage, impaired glucose transport in to the beta cell, impaired activity of key signaling pathways such as the glycerol phosphate shuttle or pyruvate carboxylase, defective ATP - sensitive channel activity, altered Na^{+}- K^{+}- ATPase activity coupled with reduced myoinositol uptake and loss of beta cell differentiation [1] .

The diagnostic criteria of diabetes: The diagnosis of diabetes is established by monitoring the elevation of blood glucose by any one of the three criteria [5].

1) A random glucose concentration greater than 200 mg /dl.

2) A fasting glucose concentration greater than 126 mg /dl on more than one occasion .

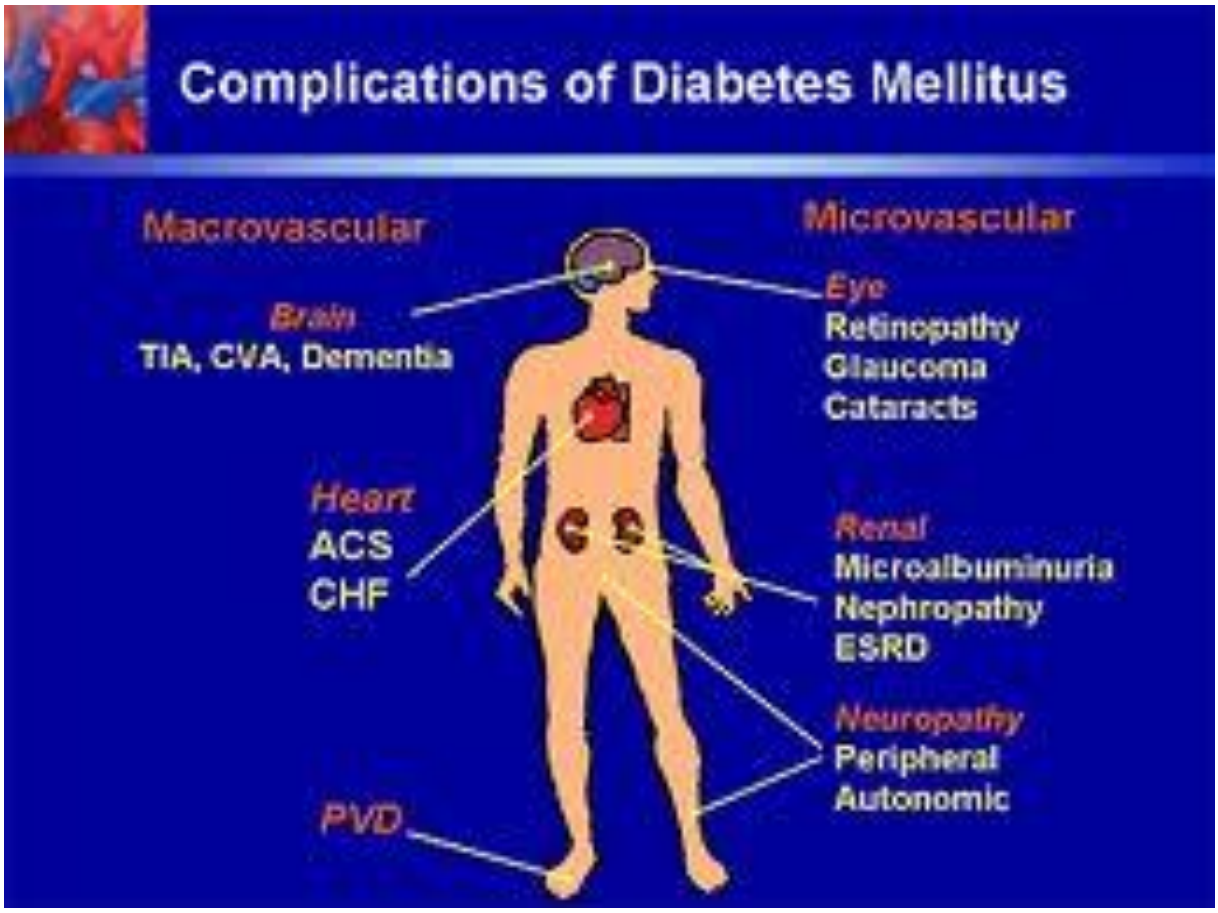
3) An abnormal oral glucose tolerance test in which glucose concentration is more than 200 mg /dl, 2hrs after intake of 75 gms of oral glucose after overnight fasting.

Diagnostic criteria for diabetes mellitus

Diabetes mellitus	Capillary whole blood (mg/dl)	Venous plasma (mg /dl)
Fasting	≥ 110	≥ 126
2 hours post glucose	≥ 200	≥ 200

Oral glucose tolerance test :

	Capillary blood (mg/dl)	Venous blood(mg /dl)
Diabetes mellitus		
Fasting	≥ 140	≥ 140
2hrs after glucose load	≥ 200	≥ 200
Impaired Glucose tolerance		
Fasting	< 140	< 140
2hrs after glucose load	160 - 200	140 - 200


Complications of Diabetes Mellitus
Macrovascular
Brain
TIA, CVA, Dementia
Heart
ACS
CHF
PVD
Microvascular
Eye
Retinopathy
Glaucoma
Cataracts
Renal
Microalbuminuria
Nephropathy
ESRD
Neuropathy
Peripheral
Autonomic

Complications of Diabetes :

The complications of diabetes are mainly related to persistent hyperglycemia. The microvascular complications in diabetes includes retinopathy, neuropathy, nephropathy and the mechanisms involved in microvascular complications are oxidative stress, glycation and activation of protein kinase C in capillary endothelial cells and pericytes.

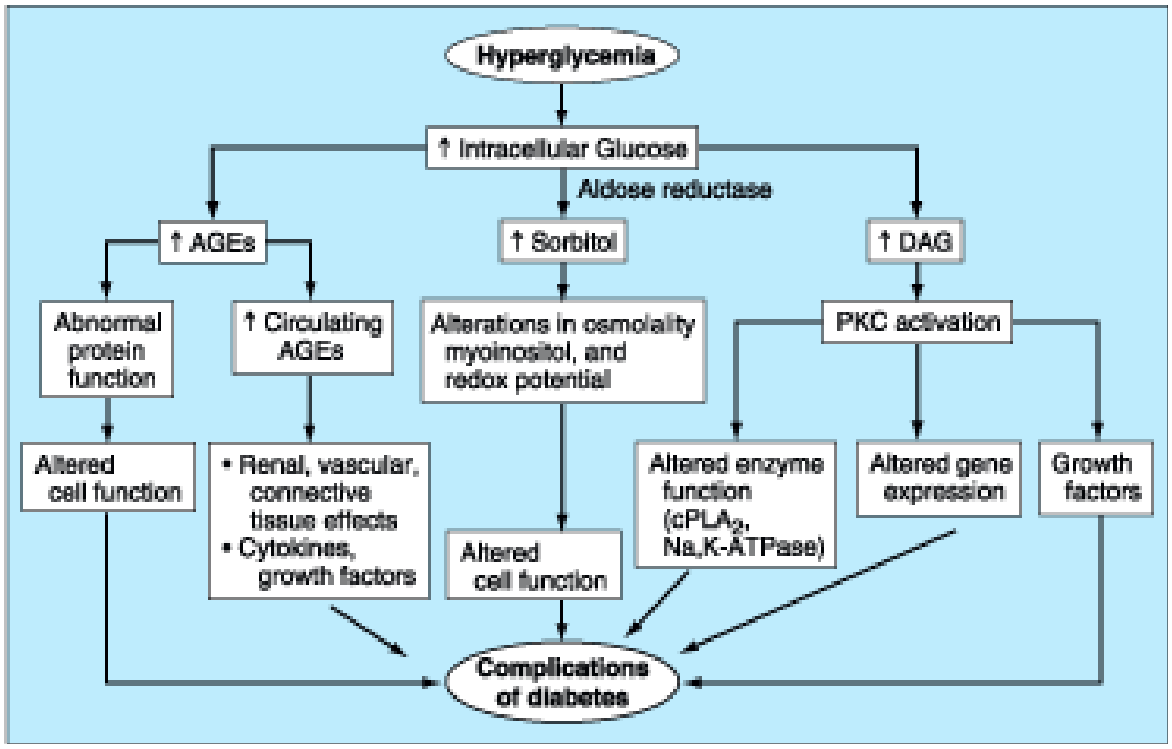
In the retina, the structural changes such as thickening of capillary basement membrane, increased vessel permeability, capillary micro aneurysm and loss of retinal pericytes, leads to the development of diabetic retinopathy.

In the renal vasculature, thickening of the glomerular basement membrane and expansion of the mesangium are the dominant morphologic features in diabetic nephropathy .

In the nerves, the hyperglycemia induced intrinsic changes in the neurons and the ischemia induced neural damage by decreased neurovascular blood flow are multifactorial causes of diabetic neuropathy.

Macrovascular complications such as coronary artery disease,cerebrovascular accidents and peripheral vascular disease are due to the atherosclerotic changes

PATHOGENESIS OF COMPLICATIONS OF DIABETES MELLITUS



in the vessel wall.

The ocular complications of diabetes are diabetic retinopathy, mononeuropathy of extra occular muscle, recurrent erosions in the cornea, neovascular glaucoma and diabetic cataract. Among these complications, diabetic retinopathy is more common [6].

Diabetic retinopathy :

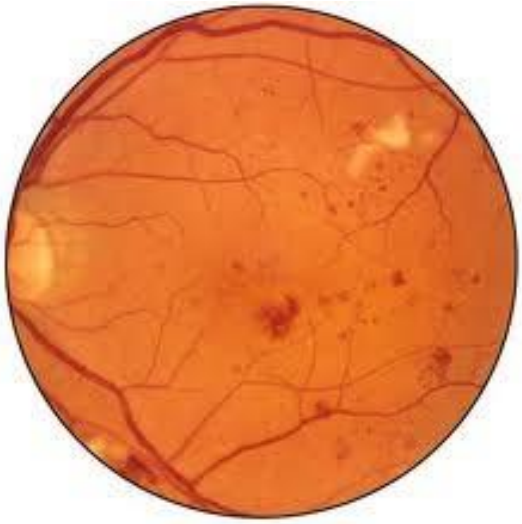
Diabetic retinopathy is a well characterized sight threatening chronic microvascular complication that eventually affects all patients with diabetes mellitus . Almost all patients with type 1 diabetes develop a retinopathy in about 15 years. In type 2 diabetes, the risk of retinopathy increases with duration and control of diabetes, associated hypertension, dyslipidemia, pregnancy, renal disease and smoking [4].

In patients diagnosed before the age of 30 years, the incidence of retinopathy after 10 years is 50 % and after 30 years is 90 % . Diabetic retinopathy rarely develops within 5 years of onset of diabetes.

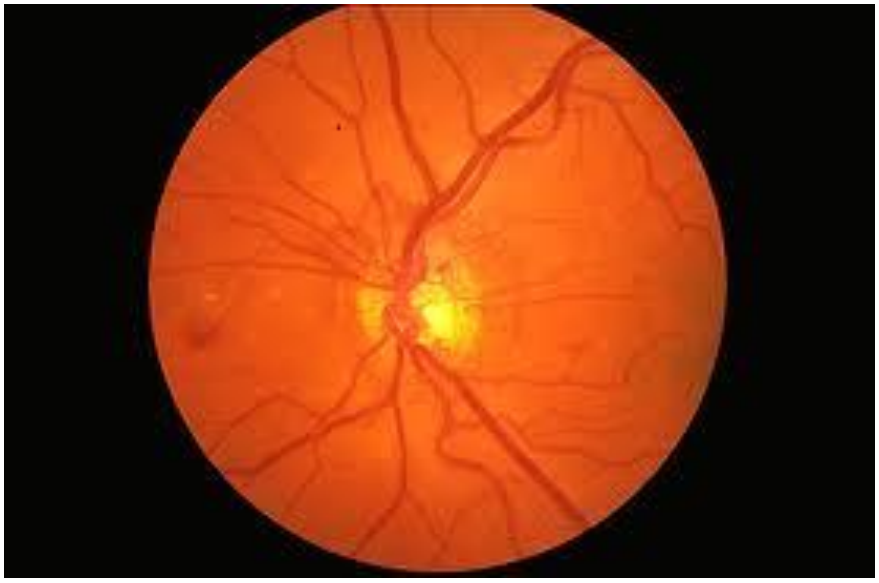
Eva Kohner's classification of Diabetic retinopathy [4]

1) Back ground retinopathy

PRE-PROLIFERATIVE DIABETIC RETINOPATHY



PROLIFERATIVE DIABETIC RETINOPATHY



2) Non proliferative diabetic retinopathy (pre proliferative DR)

3) Proliferative diabetic retinopathy

In Background retinopathy, the characteristic changes are capillary micro aneurysm, dot and blot hemorrhages, hard exudates and maculopathy. Macular oedema is the commonest cause of diminution of vision .

In pre proliferative diabetic retinopathy, multiple cotton wool or soft exudates are present, due to retinal ischemia as a result of capillary occlusion in the nerve fibre layer.

In proliferative diabetic retinopathy, the characteristic changes are neovascularization, vitreous hemorrhages and retinal detachment.

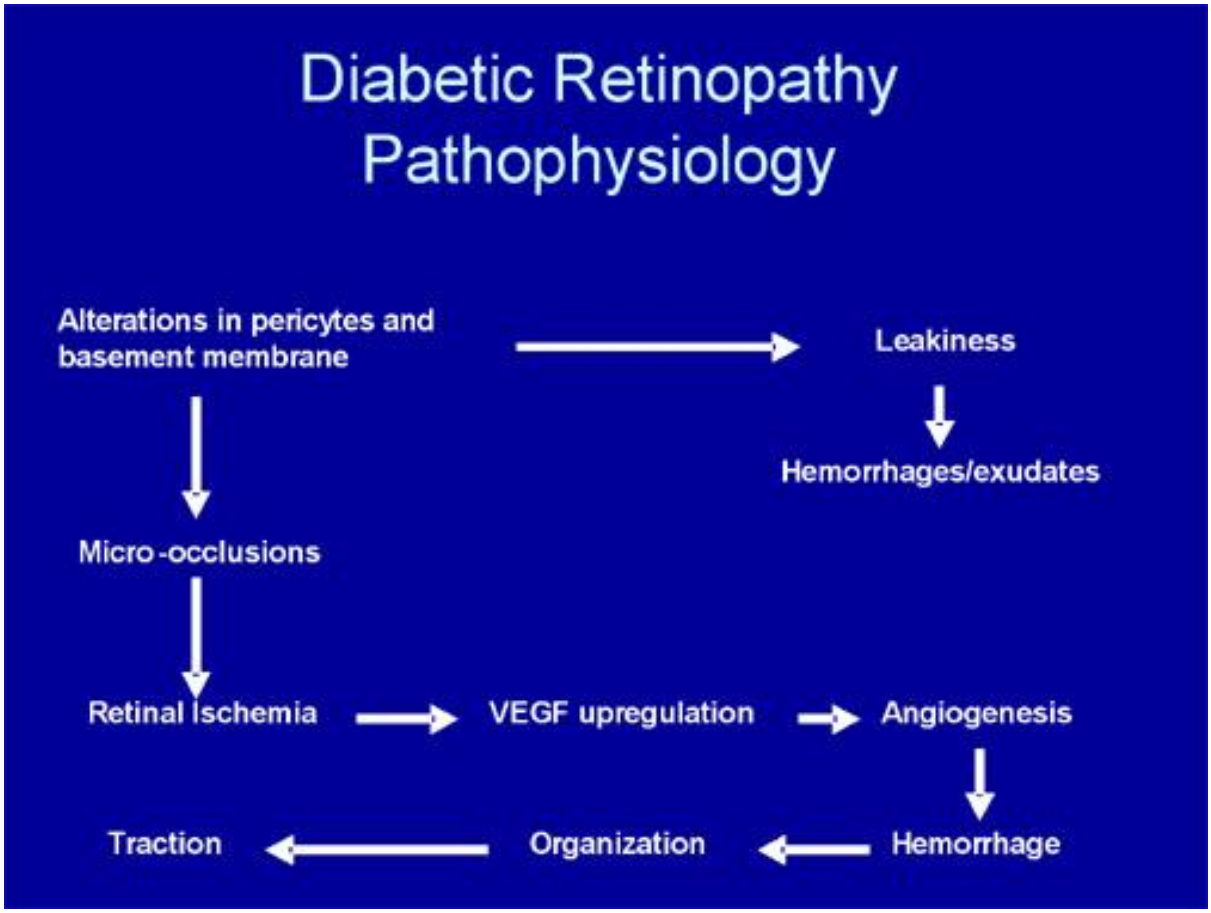
The 5 year risk of severe visual loss from proliferative DR is less than 2% and moderate visual loss from macular edema is around 12 % .

Pathophysiology of Diabetic retinopathy :

Pathogenetic mechanism for the development and progression of DR

Biochemical changes

Increase protein kinase C activity, non enzymatic glycosylation , aldose


Diabetic Retinopathy
Pathophysiology
Alterations in pericytes and basement membrane
Leakiness
Hemorrhages/exudates
Micro-occlusions
Retinal Ischemia
VEGF upregulation
Angiogenesis
Hemorrhage
Organization
Traction

reductase activity, vasoactive substances release (Endothelin, Prostanoids, Histamine, NO) , increased free radical damage, growth factor release.

Functional changes :

Altered blood flow and oxygenation, increase in the capillary permeability.

Anatomical changes :

Mural cell loss, Endothelial proliferation, Capillary closure, Micro aneurysm formation and neovascularisation[7].

Electrophysiological tests play an important role in the examination of visual system. They are used mainly to confirm the clinically suspected neurological or ophthalmological diseases like Multiple sclerosis or Retinitis pigmentosa.They also play an important role in the evaluation of unexplained visual loss without physical abnormalities, assessing the function of retina in cases of opacities in the media, quantification of visual abnormalities like uveitis and assessing the retinal and optic nerve function following trauma .

Evoked responses measures the electrophysiological responses of the nervous system to a variety of stimuli .The commonly encountered responses are visual

evoked responses (VEP), short -latency somato sensory evoked responses (SSEP) and short latency brain stem auditory evoked responses (BAER ,BAEP).

The clinical use of evoked potentials (EPs) has changed over time. Progressive advances in imaging technology have limited the frequency of evoked response studies in clinical practice.Evoked potentials explains the functionality of certain anatomical pathways of the nervous system.

VISUAL EVOKED POTENTIAL:

VEPs are electrical potential differences recorded from scalp in response to visual stimuli. Normal cortical responses are recorded if the entire visual system is intact and disturbances anywhere in the visual system can produce abnormal VEPs , there fore the localizing value of VEP is limited . It is a non invasive electrodiagnostic technique. They can be used effectively to study both normal and abnormal visual functions in the field of research. They have an excellent temporal resolution in the range of milliseconds thus permitting the study of dynamic changes occurring in the nervous system [8].

History:

In 1934, Adrian and Matthew noticed potential changes of the occipital EEG can

be observed under stimulation of light.

Ciganek developed the first nomenclature for occipital EEG components in 1961. During that same year, Hirsch and colleagues recorded a VEP on the occipital lobe (externally and internally), and they discovered amplitudes recorded along the calcarine fissure were the largest.

In 1965, Spehlmann used a checkerboard stimulation to describe human VEPs. An attempt to localize structures in the primary visual pathway was completed by Szikla and colleagues.

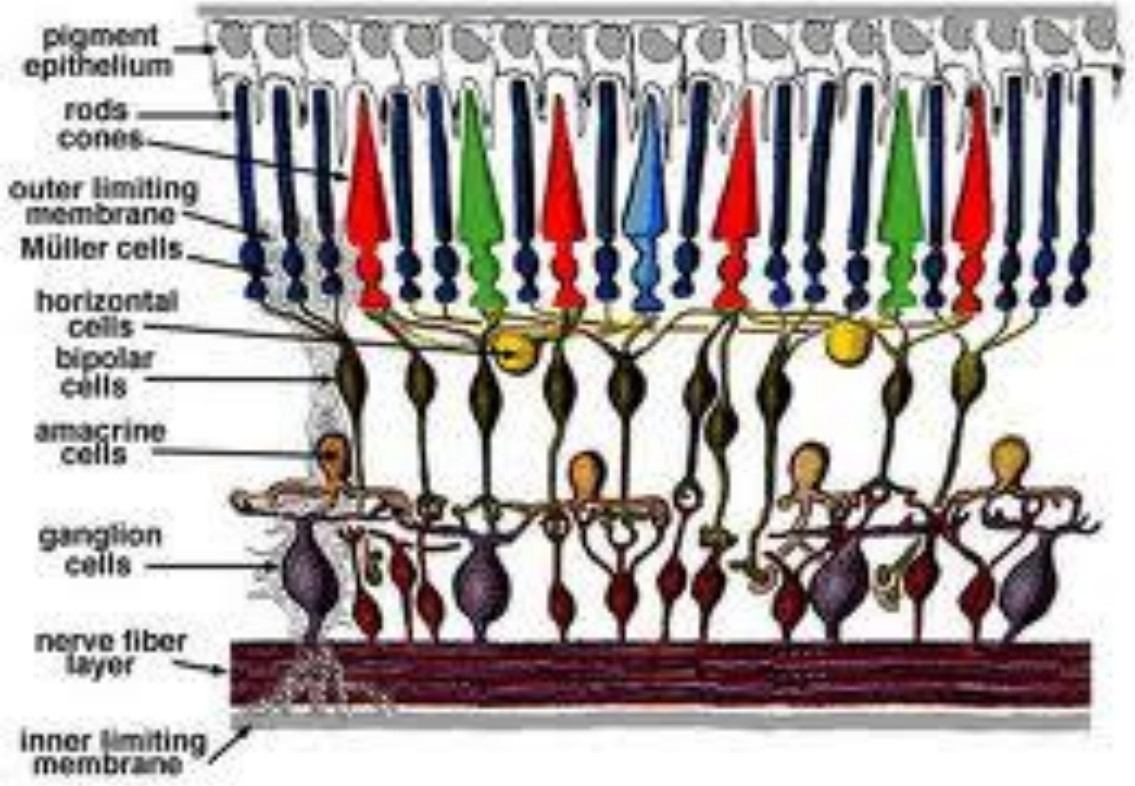
Halliday and colleagues completed the first clinical investigations using VEP by recording delayed VEPs in a patient with retrobulbar neuritis in 1972. A wide variety of extensive research to improve procedures and theories has been conducted from the 1970's to today.

Methods of VEP:

The commonly used techniques for performing VEP are pattern reversal VEP (PR-VEP), pattern onset/offset and flash VEP (FVEP).

In pattern reversal VEP the subject is asked to focus on a checker board pattern of

LAYERS OF RETINA



alternating black and white squares displayed on a monitor in which the colors interchange at fixed frequency. In pattern onset/offset VEP the checker board pattern is exchanged with a diffuse grey background with no change in luminance. FVEP is a technique in which repeated flashes of light of fixed luminance, frequency and color are given as stimuli, using xenon flash tube.

Pattern reversal is the prefered stimulus for most clinical purposes. It shows less variations in waveforms and their timing than other techniques. Pattern onset/offset stimulus is best suited for detection of malingering and for use in patient with nystagmus. FVEPs are used only in cases of poor optics, poor cooperation and poor vision

Anatomical basis of visual evoked potential

The optic nerve joins the retina with the brain. The receptor or end organ through which visual impulses are mediated are rods and cones of retina.They are stimulated by light impulses and synapse with inner nuclear or bipolar layers , the cells of which in turn synapse with ganglion cell layer . The axons of the ganglion cells form the optic nerve, which extends from the retina to optic chiasma and is about 5 cm long, of which 3.5 cm is in the orbit and 1.5 cm in the optic foramen

and within the skull. Approximately 1 million fibers of optic nerve are unmyelinated in the retina and optic nerve head but these become myelinated as these pass through lamina cribrosa. The two optic nerves unite at optic chiasma. The fibers from the temporal half of the retina are situated in the temporal half of the nerve and pass through the chiasma without crossing and terminate at the ipsilateral cortex, but the fibers from the nasal half of the retina decussate at chiasma and terminate at the contralateral cortex. The optic tract starts from the optic chiasma and terminates in the dorsal lateral geniculated nucleus located at the dorsal end of thalamus within the lateral geniculate bodies. Fibers carrying impulses from the upper portion of the retina terminate in the ventromedial segment and those from the lower portion in ventro lateral segment of LGB. The ipsilateral temporal fibers terminate in layers 2, 3 and 5 whereas the contralateral fibers terminate in layers 1, 4 and 6. Approximately 50 % retinal ganglion cells decussate at the optic chiasm to innervate the contralateral lateral geniculate nucleus.This results in the monocular VEPs having similar amplitudes at the cortex. Neurons originating from LGB form optic radiations (Geniculocalcarine fibers) pass posteriorly to terminate in the striate cortex (area 17). The macular fibers occupy the larger portion of occipital lobe at the pole in a wedge shaped area. The upper half of retinal fibers relay superior and the lower

half inferior to the calcarine fissure.

The P_{100} wave form of VEP is generated in the striate and peristriate occipital cortex is due to the activation of primary cortex on giving pattern or flash stimulation. There is increased metabolism in the primary visual area and as well as in the visual association area (area 18 and 19). The regional cerebral blood flow increases with stimulation rate up to 8 Hz and gradually declines there after. VEP is primarily a reflection of activity originating in the central 3 - 6 degree of the visual field, which is relayed to the surface of occipital lobe.

Cells in the striate cortex are arranged retinotopically as in the LGN, thus, two cells located next to one another in the cortex process information from areas of visual field located next to one another. There is a significant divergence of information from the macula to the cortex. Approximately half of the striate cortex is devoted to processing information from central 10 degrees of visual field. Most of the cortical cells are devoted to the macula, therefore VEP is principally a macular response [9].

VEP is a sensitive indicator of optic nerve function. It is an evoked electro physiological signal that is recorded at the scalp in response to visual stimuli. The

responses are smaller than ERG responses, typically measuring 5-10 micro volts in amplitude. Averaging of the recorded signal over a given time period after repeated stimulation can help in extraction of VEP from the background EEG activity.

The visual system processes information along with multiple parallel channels. The separation of visual information starts at the neuronal circuitry of the retina where particular features such as color, contrast, luminance and other parameters of the stimulus are extracted and processed. It has been suggested that seven parallel channels of ganglion cells process visual information in the primate retina. These retinal neurons send central projections to the LGB.

Dorsal lateral geniculate nucleus is divided into

1) Magno cellular layer

2) Parvo cellular layer

Layer I and II are called magnocellular layers because they contain large neurons. They receive the input from large type of Y retinal ganglion cells. This provides a rapidly conducting pathway to the visual cortex [10] .

The parvocellular layers (layers III, IV, V, VI) contain large number of small to medium sized neurons, these neurons receive input from the type X retinal

ganglion cells that transmit color and generate point – point spatial information but only at a moderate velocity of conduction. So the magnosystem is involved primarily with motion analysis. The parvocellular system shows a preference for high spatial frequency stimuli.

Visual pathways emphasizes the extent to which the neocortex is involved in parallel visual processing. There are two pragmatic principles that can be derived from the above data.

1) Visual stimuli not only activate the occipital lobes but also involve large areas of temporal and parietal lobes.

2) Different structures of the retinal and visual pathways can be preferentially activated by changing the characteristic of visual stimuli.

The first principle indicates that VEPs can be recorded from a large region of the scalp, essentially from the vertex to the inion. .

BASIC TECHNOLOGY:

National federation of clinical neurophysiology (IFCN) described the standards of basic technology for recording VEPs [10]. The principle of recording VEP are simple. A visual stimulus is presented to the subject for a selected number of

times and the cerebral responses are amplified, averaged by a computer and displayed on an oscilloscope screen or printed out on paper. For neurological purposes, VEPs are generally elicited by monocular stimulation of each eye while the other is covered with a patch. Visual stimuli can be either patterned stimuli or unpatterned stimuli. Unpatterned stimuli most frequently consists of stroboscopic flashes. Patterned stimuli consists of specific pattern such as checks or bars on which the subject is required to fixate. The two most frequently used patterns are checks and gratings. The pattern should be achromatic (black and white). The size of the individual checks should be expressed in terms of visual angle.

Visual angle β is expressed as $\beta = \tan^{-1}(W/2D) \times 120$ where β is visual angle in minutes of arc; W is the width of checks in millimeters and distance of pattern from the corneal surface in millimeters. The measurement in cycles per degree define the spatial frequency of stimulus. Measurements of the visual cycle in minutes of arc can be converted to cycles per degree by the formula $C / \text{degree} = 30 / W$.

The most frequent method of presentation of the stimulus is by reversal of checkerboard pattern. The black checks become white and vice versa so that

there is no change in the total luminance (Iso luminance) of the pattern. Isoluminance is important in preventing light scatter in the retina. The VEP is affected by the stimulus intensity. Intensity of stimulus is defined by luminance. The mean luminance of the field of stimulation is expressed by the formula

$$Lmax + Lmin /2$$

Where L max indicates the maximum and L min indicates minimum luminance of the field. A desirable mean field luminance is at or above $100cd/m^2$. Another important parameter that may modify VEP is contrast. Contrast is defined as difference between bright and dark portion of a pattern. It is expressed by the formula $C=\{(Lmax – Lmin)/(Lmax +Lmin)\}x\ 100$.

The IFCN recommends that a minimum of three stimuli be used for testing and suggests the following parameters.

1) Pattern stimuli consisting of either checks or gratings
2) Size of the pattern elements 14’-16’, 28’-32’, 56-64’
3) Full field size at least 8 degrees (1degree=60minutes)

4) Contrast between 50 – 80 percent

5) Rate of presentation 1 Hz (producing a reversal every 500 m sec)

6) Mean luminance of center field at least 100cd/m2

7) Background luminance under photopic condition at least 30 -50 c d/m2

8) The distance between subject eye and screen should 70-100cm

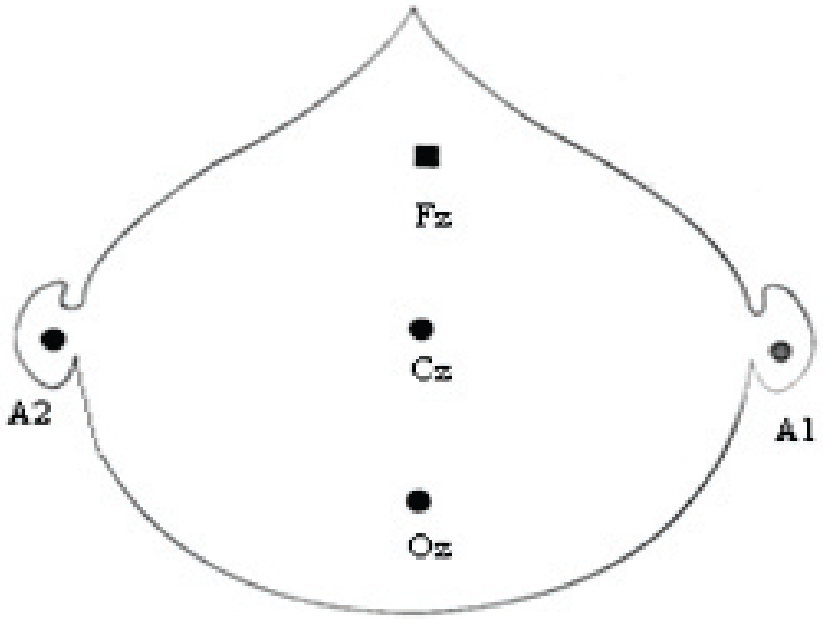
The IFCN suggests a two channel montage, Oz – FPz and Oz-A_1- A_2 (linked ears), with the ground placed at C_Z for recording VEPs. The band pass low cut filters are set at 1-3Hz and high cut filters at 100 - 300 Hz, on reducing the high cut filters the P_{100} latency decreases. So the filter setting should be kept constant. The subject fixates on the center of the pattern during stimulation. The responses are recorded at least twice to ensue their replicabity.

NORMATIVE DATA :

VEPs to a pattern-reversing checker board (the most frequently used stimulus in clinical laboratories) consists of a set of sequential wave forms. For recording VEP, standard disc EEG electrodes are used. The skin is prepared by abrading and degreasing.The recording electrode is placed at Oz using conducting jelly

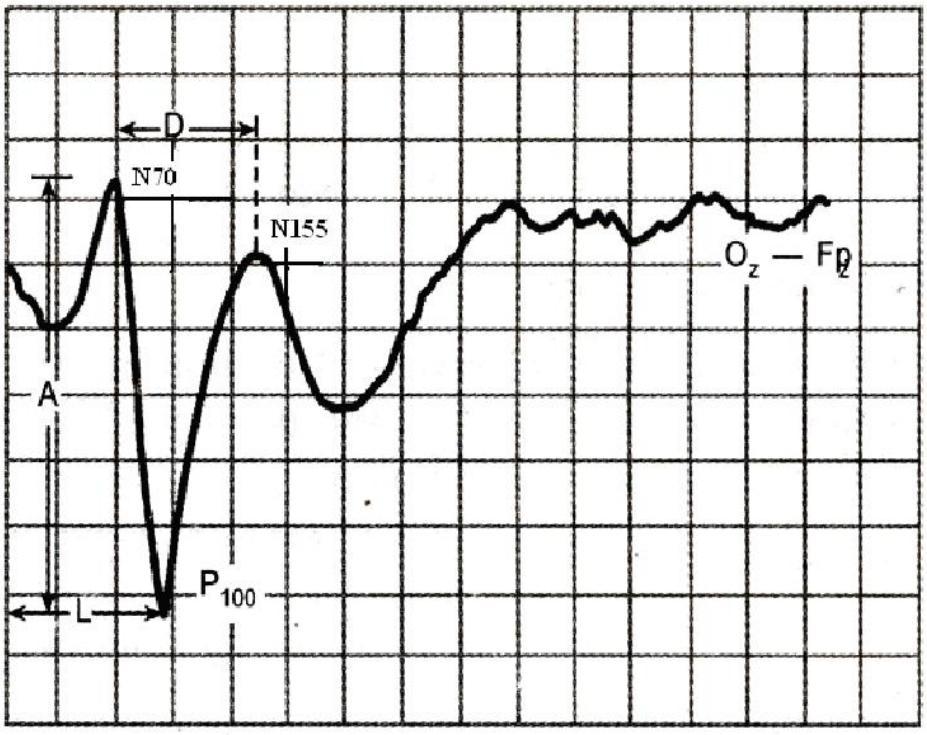
or electrode paste asper 10-20international system of EEG electrode placement. The reference electrode is placed at FPz or 12 cm above the nasion. The ground electrode is placed at vertex. The electrode impedance should be kept below 5 k Ω. These electrode positions are used to ensure reproducible electrode placement in serial studies and do not represent respective cortical areas. An amplification ranging between 20,000 and 100,000 is used to record pattern shift visual evoked potentials (PSVEP). Sweep duration should range between 250 and 500 miliseconds. A short sweep duration alters the P_{100} wave forms, generally 100 epochs are averaged. The averaging some time may have to be increased to 200 –500 epochs to ensure a clear potential. The mono ocular full field stimulations is used always, so that the test is most sensitive to lesions of optic nerve anterior to chiasma. The VEP wave form is the sum of many wave forms generated simultaneously by various areas of retinotopically organized occipital cortex. The negative wave form is denoted as "N" and positive deflection as "P" which is followed by approximate latency in milli seconds. The commonly used wave forms are N_{70}, P_{100} and N_{135}. The primary basis for interpretation of VEP is measurement of latency of P_{100} component (the normal P wave latency is 100 milliseconds in normal persons) after stimulation

POSITION OF RECORDING ELECTRODES



Oz - active, Fz- reference electrode, Cz- ground electrode
(The subscript z indicates a midline position)

NORMAL TRACING OF VEP WAVE FORMS



of each eye separately. After the absolute P_{100} latency for each eye is measured, the inter eye P_{100} latency difference is determined . Comparison of these values with normative laboratory data will indicate normal or abnormal nature of response. Unilateral prolongation of P_{100} latency after full field mono ocular stimulation implies an abnormality anterior to the optic chiasma on that side. Bilateral lesions either anterior or posterior to the optic chiasma or a chiasmal lesion will cause bilateral delay of P_{100} latency.

Normal values of visual evoked potential [9]

Parametes P_{100}	Mean ± SD
Latency (ms)	96.9± 3.6
R-L (ms)	1.5 ± 0.5
Amplitude (μv)	7.8 ± 1.9
Duration	55.9 ± 7.7

Variables influencing VEP [9]

Age:

Age influences the latency of P_{100} at a rate of 2.5 ms / decade after 5^{th} decade. This has been attributed to age-related changes in both retina and the rostral part of visual system. The changes which include ganglion cell loss, demyelination, axonal swelling, nerve fiber loss are due to changes in the neuro transmitter function and increased synaptic delay in senescence. The amplitude of VEP remains stable in adult life.

Gender : The P_{100} latency is longer in adult males compared to females. This is due to larger head size and lower core body temperature in males. In the age group below 19 years, P_{100} latency does not vary with sex although a longer latency has been reported in girls. The P_{100} amplitude is greater in females compared to males, cause is unknown probably due to hormonal influences have been suggested.

Eye dominance:

P_{100} wave obtained by stimulating the dominant eye is shorter and amplitude greater compared to the non dominant eye. This is due to neuroanatomic asymmetries of human striate cortex.

Eye movement: Eye movement reduces the amplitude of P_{100} but its latency is not affected. The patients with nystagmus having a normal visual pathway also have a normal P_{100} latency.

Visual acuity:

P_{100} latency remains normal in spite of pronounced diminution of visual acuity. The latency of P_{100} is reported to be normal with visual acuity as low as 20/120; however, the amplitude decreases with further reduction of visual acuity.

Drugs:

Drugs producing pupillary constriction such as pilocarpine can increase P_{100} latency, which is attributed to decreased area of retinal illumination. The mydriatics result in an opposite effect.

Reproducibility and Variability:

During mental activity such as problem solving, the P_{100} latency has been reported to decrease and the amplitude increase. An unmotivated patient may alter the P_{100} latency or amplitude by closing the eye, gazing off the screen, converging in front of target or even his nose. Although the VEP wave forms are reproducible, they have an inherent intra individual variability.

Abnormal visual evoked potentials

Abnormalities of VEPs have been described in many disorders of optic nerve, chiasma and retro chiasmatic visual pathways. The VEP can be considered abnormal when the latency of P_{100} wave is outside the 95-99 percentile boundaries established for normals. Delay or absence of N_{70} peak is more difficult to evaluate, because this component is variable in different subjects. The most frequent abnormality is characterized by a normal amplitude but a prolonged latency of N_{70} and P_{100}. The intereye latency difference is useful to locate the side of the lesion , the latency difference between the two eyes greater than 10 ms is indicative of pathology on that side with longer latency.

The commonest cause of prolonged of P_{100} latency is demyelination in the optic pathways where the amplitude of the P_{100} remains normal. The ischemic optic neuropathy leading to axonal loss produces the normal P_{100} latency and decreased amplitude. Optic nerve compression produces segmental demyelination and axonal loss resulting in both latency and amplitude abnormalities in VEP. Diabetic retinopathies, maculopathies, retinal infarcts and scars are associated with abnormal VEPs [9].

Causes of abnormal visual evoked potentials [8]

Ocular disease:

Major refractory errors, lens and media opacities, Glaucoma, and Retinopathies.

Compressive lesions: Extrinsic tumors, Optic nerve tumors.

Non compressive lesions :

Demyelinating disease, Ischemic optic neuritis, Nutritional and toxic amblyopias.

Diffuse central nervous system disease: Adrenoleukodystrophy, Spinocerebellar degenerations and Parkinson's disease.

Studies of visual evoked potential in diabetes mellitus

Pan CH , Chen SS conducted the study of pattern shift visual evoked potentials on 46 cases of NIDDM and 13 cases of IDDM showed the prolongation of all peak latencies [11] .

Fierro B et al studied in a group of 35 patients with 10 or more years of duration of diabetes, the P_{100} latencies of VEP were found significantly prolonged in 10 (28%) patients [12].

Parisi V et al conducted the study of VEP after photo stress in insulin dependent diabetic patients with or without retinopathy, the study showed a prolonged P_{100} latency which was significantly higher in IDDP and IDDP-WR than in control groups [13] .

Dolu H et al conducted the study in 51 patients with type 2 DM showed prolongation of P_{100} latency of VEP related to duration of disease [14.]

Karlika D et al studied the use of visual evoked potential in 45 type 1 DM patients to detect a pre diabetic form of diabetic retinopathy.The study showed the P_{100} latency values increases progressively as the year passes. They concluded that increase in VEP latency are a direct sign of retinal ganglion cell damage [15].

In a study on 35 diabetics and controls by puvendran k, Devathasan G and wong pk, it was found that latency was increased by more than one standard deviation in 13 diabetics (81%) and more than three standard deviation in 10 diabetics (62.5%) and often associated with marked reduction in amplitude. They found that extent of optic nerve involvement in 16 diabetics without development of retinopathy and other ocular diseases [16].

Dr Sami ulus, Turkey studied the VEP and its relation with HbA1c in children with IDDM. It was found that VEP latencies of the diabetic children in both eyes were significantly prolonged when compared with control group. There was a positive correlation of prolongation of P_{100} latency with HbA1c [17].

The study was conducted by Pozzessere G et al in both type 1 and type 2 diabetic patients. It was found that VEP latencies were significantly prolonged and these prolongation occurs only a few years after clinical diagnosis and before the appearance of overt complications and seem to be correlated with metabolic control status [18].

In other study conducted by Ponte F, Giuffre G, Anastasi M, Lauricella M , in 62 type 1 diabetics showed the delayed latencies of VEP on pattern reversal stimulation . A positive correlation was found between the VEPs latencies and duration of diabetes [19].

A longitudinal study in NIDDM conducted by Moreo G, Mariani E, Pizzamiglio G, Colucci GB to assess the possible progression of neurological abnormalities overtime and VEP in predicting the diabetes related optic pathway disease. It was found that the peak P_{100} wave latencies were

significantly delayed in diabetics compared with the control subjects and the VEP alteration were stable over time and correlated positively with metabolic control [20].

Collier A, Mitchel JD and Clarke BF conducted the study on 22 insulin dependent diabetics aged 20-35 years of whom 5 did not have retinopathy, 11 had back ground retinopathy and 6 had proliferative retinopathy and it was found that all patients with proliferative retinopathy showed delayed VEP latencies [21] .

Yaltkaya K, Balkan A, Baysal conducted the study to investigate the possible effects of the disease on central nervous system by means of pattern shift VEP. It was found that in diabetic patients latency prolongation in P_{100} and N140 components were observed and in patients with long standing diabetes mellitus, the incidence of VEP abnormalities were found to be high [22].

Comi G studied the abnormalities of central afferent and efferent pathways, by evoked potential studies in diabetic patients and it was found that VEP latencies were abnormal in central nervous system disease and peripheral neuropathy but latencies were abnormal in central nervous system disease and peripheral

neuropathy but VEP can be abnormal even in patients without retinopathy [23].

Verotti A et al conducted the VEP study in young persons with diabetes in basal condition and after photo stress in 30 newly diagnosed patients with diabetes and showed that the P_{100} latency was significantly delayed in patients with diabetes compared with control group and measurements were repeated after 6 months, when all diabetes had achieved good metabolic control, a complete normalization of parameters was observed suggest that early functional abnormalities of the optic nerve can be detected at the onset of diabetes and the glycemic control reverses these abnormalities [24] .

Tamas T.Varkonyi et al conducted the study in type 1 diabetes and found that VEP measurements were impaired even at an early stage of the pathogenetic process [25].

Michel Algan et al conducted the VEP test in 50 adult type 1 and 19 type 2 diabetics and in 54 controls. P_{100} wave latency was significantly longer in diabetic patients ($P<0.001$) found that there was no correlation between P_{100} latency and type or duration of diabetes or quality of metabolic control [26] .

Ziegler Oet al conducted the study of VEP in poorly controlled diabetic patients

after short-term metabolic control, to determine whether short term strict control of blood glucose can improve abnormal VEP in 12 poorly controlled diabetic patients before and after at least 3 days of near normoglycemia obtained by continuous insulin infusion. The result showed that P_{100} latencies were longer in diabetic than in control subjects ($P< 0.01$) and after 3 days of blood glucose control, the mean P_{100} latencies were significantly shorter but were still significantly longer than control values. There was no correlation between fall in blood glucose and improvement in VEP [27].

Eliya et al did a study of color VEP in children with type 1 diabetes with relation to metabolic control. The study showed that VEP latencies were not associated significantly with HbA1c. However, pubertal children with type1DM had delayed VEP latencies when compared with the pre pubertal children with type 1 DM [28].

Deepika chopra, Mridu gupta, Manchan K.C, Ram sarup sharma , Rajender sing sidhu conducted a study in patients of type 2 diabetics . The result showed that significantly prolonged N_{70}, P_{100} latencies in diabetic patients and also significant correlation between the delay in P_{100} latency and the duration of disease [29].

Vincenzo parisi et al conducted a study of VEP in newly diagnosed IDDM

patients. The results showed that VEP P_{100} latencies significantly delayed ($P<0.01$) in diabetics, compared with control subjects [30].

Raman PG, Sodani A, George B conducted a study of VEP changes in 25 diabetic patients. The result showed that P100 latencies and amplitude were significantly prolonged ($P=0.001$). A positive correlation was documented between glycemic control and prolonged P_{100} latencies. There was no correlation between presence and absence of peripheral neuropathy and delay in P_{100} latencies [31].

Costache D, Damianc, Iancau M conducted the VEP recording in 24 diabetic patients with retinopathy and it was noticed that delay of P_{100} wave with inconstant presence of N_{75} and N_{135} waves [32].

Algan et al conducted the VEP testing in 50 adult type 1 and 19 type 2 diabetic patients and in 54 controls. The results showed that P_{100} wave latency was significantly longer in diabetic patients ($P<0.001$) [33].

Cirillio D et al conducted a study of VEP in 30 IDDM children and adolescents. The result showed that 30% of subjects had evidence of significant abnormalities [34].

Fiona M.E Ewing, Ian J.Deary, Mark W.J.Strachan and Brian M.frier conducted

the electrophysiological study in diabetic patients and they concluded that good evidence exists for abnormalities occurring in P_{100} response in people with diabetes before the development of overt retinopathy ranging from the newly diagnosed patients with IDDM to those with diabetes of longer duration [35].

Filiz A frashi et al performed the VEP recording in 20 IDDM patients and compared with age matched controls using pattern reversal VEPs. The study revealed that mild prolongation of P_{100} latencies in IDDM patients compared to

controls (99.6 ± 7 ms) [36].

Radha shenoy et al conducted a VEP study in uncontrolled type 1 & type 2 diabetic patients before and after pan retinal laser treatment. The study results showed that P_{100} latency increased before and after treatment. The P_{100} amplitude was not changed before treatment but significant decrease in P_{100} amplitude after treatment [37].

Shinoda kei et al conducted a study in a patient with proliferative diabetic retinopathy with development of ischemic optic neuropathy after pars plana vitrectomy. On the first post operative day, the patient noticed a defect in visual field in the operated eye. VEP in that eye had slightly delayed latency and

electroretinography showed almost normal response in the operated eye [38].

Uberall M.A, Chr.Renner, Parzinger E, Wenze D perfomed a VEP study in 29 type 1 diabetic children and adolescent compared with 29 controls. The IDDM subjects showed highly significant latency prolongations ($P<0.001$) for P_{100}, N_{150}, P_{200} and P_{300} compared with healthy controls [39].

Pioter rajewski et al conducted a VEP study in 90 patients with type 1 & 2 diabetes. Abnormal VEP were common in patients with clinical signs of peripheral neuropathy ($P=0.004$), insufficient glycemic control ($P<0.02$), type 2 diabetes ($P= 0.004$) and in elderly patients ($P < 0.001$) [40].

Marta Wysocka - mincewicz et al evaluated the coexistence of abnormalities in the peripheral nervous system and VEP in children with type 1 diabetes. There was a significant prolongation of P_{100} latency ($P<0.05$) among the children with polyneuropathy verses the children without poly neuropathy [41].

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY DESIGN:

This is a combined cross sectional and case control study.

STUDY PLACE AND STUDY PERIOD:

This study was carried out in the Research laboratory of the Department of Physiology, Coimbatore medical college, Coimbatore. The study period extended from June 2010 to June 2011. The approval of the Ethical committee was obtained prior to the commencement of the study.

STUDY SUBJECTS:

A total of 80 subjects were included in the study of which 40 were diabetic patients (both type 1 and type 2) and 40 were control groups. They were of 30-70 years of age group. All the cases of diabetic mellitus were taken from diabetic clinic of Coimbatore Medical College Hospital and the controls were taken from the general population. The study subjects of both sexes were divided in to two groups.

Group I - 40 controls, age and sex matched healthy individuals.

Group II – 40 diabetic patients.

Group II $_{A}$ - 20 type 1 diabetic patients

Group II $_{A1}$ - 0 - 10 years of duration of diabetes

Group II $_{A2}$ - 11 – 20 years of duration of diabetes

Group II $_{A3}$ - more than 20 years of duration of diabetes

Group II $_{A4}$ - patients with good glycemic control

Group II $_{A5}$ - patients with poor glycemic control

GROUP II $_{B}$ - 20 type 2 diabetic patients

Group II $_{B1}$ - 0 – 10 years of duration of diabetes

Group II $_{B2}$ - 11 - 20 years of duration of diabetes

Group II $_{B3}$ - more than 20 years of duration of diabetes

Group II $_{B4}$ - patients with good glycemic control

Group II $_{B5}$ -Patients with poor glycemic control

INCLUSION CRITERIA:

Diabetic and normal subjects of both sexes in the age group of 30 – 70 years were included. Detailed ophthalmological check up of all patients was done, which included visual acuity, recording of ocular tension and fundus examination under full mydriasis.

EXCLUSION CRITERIA:

Patients having a history of any disorder which could influence the interpretation of results such as

Retinopathy

Glaucoma

Cataract

Hypertension were excluded from the study.

MATERIALS USED FOR THE STUDY:

1. NeuroPerfect EMG 2000 system – to collect, analyze, print and store a visual evoked potential data.

2. Autoanalyser – to analyse plasma sugar and HbA1c levels.

RMS EMG EP MARK II MACHINE

METHODOLOGY:

The study was carried out after explaining the procedures in detail and getting informed consent from the subjects. The study was approved by the Ethical committee of Coimbatore Medical college. The study protocol involved

1. Recording of a detailed history including history and duration of diabetes, history of hypertension, coronary artery disease, glaucoma and cataract from the study subjects.

2. A thorough clinical examination of the study subjects.

3. Measurement of blood sugar and HbA1c level:

Blood samples were collected by sterile technique using disposable syringes. Fasting samples were collected in the morning after 12 hours of fasting from 40 diabetics and 40 control subjects. Post prandial blood sugar samples were collected 2 hours after breakfast. Blood samples were collected from 40 diabetic patients to estimate HbA1c level. Fasting and post prandial blood glucose and HbA1c were estimated using an autoanalyser.

Glycated Hb testing :

Hemoglobin is normally glycated with glucose to form HbA1c. This glycation is

irreversible and the level of HbA1c present in the blood increases with high blood glucose levels. So it provides an index of blood glucose level over the previous 6 to 12 weeks. Normal value of HbA1c is < 6.5.

Autoanalyser

Autoanalyser is an open, fully automated, discrete, patient prioritized, random access, computerized analyzer. It is intended for in vitro quantitative determination of a wide range of analytes in various body fluids. The analyzer operation is very user friendly with minimum handling required from the operator. The working unit of the analyzer comprises a basic operating unit with an intelligent photometer and sophisticated robotics combined with an operating console and a central processing unit. The photometer uses a flat field polychromator for measuring the optical densities of reaction mixtures. The results thus obtained were tabulated and analysed.

4. Procedure for recording visual evoked potential:

Pattern- shift visual evoked potential test was performed in a specially equipped electro diagnostic procedure room (darkened, sound attenuated room). The patients were explained about the test and should avoid hair spray or oil before the test. The

PHOTOGRAPHS SHOWING THE METHOD OF RECORDING VEP

patient were seated comfortably one meter away from the pattern – shift screen. Subjects were placed in front of a black and white checker board pattern displayed on a video monitor. Standard silver chloride electrodes of 1cm diameter were used for recording. International 10 – 20 system nomenclature was used for recording electrode position. The electrodes were applied to the scalp using conduction jelly after thoroughly cleaning the area. Recording electrode was placed at Oz position, reference electrode was placed at Fz and the ground electrode placed at M1position using conducting jelly. Subjects were given 5 minutes to get acquainted with laboratory environment before carrying out the actual procedure. The pattern – shift screen checks changes alternatively black/white to white/ black at a rate of approximately twice per second. Every time the pattern changes, patient's visual system generates an electrical response which was detected and recorded by surface electrodes. The patient was asked to focus his gaze on to the center of the screen. Each eye was tested separately, while the other eye was being covered with an opaque patch. The participants were watched by the examiner for any eye movements or attention lapse during the procedure. This has been considered as standard technique for the present study.

RESULTS

RESULTS

The present study was conducted in the Department of physiology, Coimbatore medical college, Coimbatore. 40 diabetic individuals and 40 controls were selected for the study. One way ANOVA & Student 't' test were used to assess the statistical significance. All data is expressed as mean ± S.D.The mean value, standard deviation of VEP parameters of right and left eye in the Groups I, IIA and IIB are shown in the (Table 1-4)

The data revealed that:

The mean value of the P_{100} latency was significantly delayed in Group II_A and Group II_B patients as compared to that in Group I subjects. There was no significant prolongation of N_{75} and N_{145} latencies in Group II_A and Group II_B patients as compared to Group I subjects. (Table – 1/ Fig:1,2)

The mean value of the N_{75}-P_{100} amplitude was not significantly decreased in Group II_A and Group II_B patients as compared to Group I subjects. (Table - 1/ Fig:1,2)

Comparison of VEP responses was done between Group II_A and Group II_B. There was no statitically significant difference found between these two groups.

(Table - 2 / Fig: 3,4)

The patients whose HbA1c was studied; were divided in to two groups, one with HbA1c ≤7% and second with >7% in order to assess the relation between long term glycemic control and altered VEPs. (Table: 3,5-12 / fig:5-16).

The results showed that P_{100} latencies were significantly prolonged in both $GroupII_{A5}$ and $GroupII_{B5}$ patients whose HbA1c value is >7%.(Table - 3,5 & 9/ fig: 5,6,7,8,9 & 13).

The N_{75} latencies in both $GroupII_{A5}$ and Group II_{B5} patients showed prolongation with poor glycemic control (HbA1c >7%) but the statistical significance could not be demonstrated. (Table:3,6 & 10 / fig: 5,6,7,8,10 & 14).

The N_{145} latency and N_{75}- P_{100} amplitude in both $GroupII_{A5}$ and Group II_{B5} were not prolonged with poor glycemic control (HbA1c >7%). (Table -3,7,8,11 & 12/ fig: 11,12,15 & 16). A positive correlation was found between prolonged P100 latencies and glycemic control in Group II_{A} and Group II_{B} Patients, but, statistically significant differences was not found between these two groups in relation to glycemic control.(Table - 3 / fig:5,6,7 & 8).

The study groups were analysed to find out the correlation between prolongation of VEP latencies and duration of diabetes. The mean value of the P_{100}, N_{75}, N145 and N_{75}-P_{100} amplitude were shown in(Table : 4 / fig : 17-21).

The P_{100} latencies in Group II $_A$ and Group II $_B$ showed siginificant delay with increased duration of diabetes(Table:4 / Fig: 17- 21).

The N_{75}, N_{145} latencies and N75-P_{100} amplitude values were not prolonged with increased duration of the disease (Table:4 / Fig: 17- 21). A positive correlation was found between prolonged P100 latencies and increased duration of disease but, there was no statistically significant difference observed between Group II_A and Group II $_B$ in relation to duration of disease. (Table : 4 / Fig: 17- 21)

TABLE: 1 P100, N75, N145 LATENCIES AND N75-P100 AMPLITUDE IN GROUP I & GROUP II

VEP PARAMETERS	Group I		Group IIA		Group IIB		P VALUE	
	Right eye Mean± SD	Left eye mean±SD	Right eye Mean± SD	Left eye mean±SD	Right eye Mean± SD	Left eye mean±SD	Right Eye	Left Eye
P100 ≤100	97.9 ± 1.93	98.13±1.59	98.37±1.81	97.97±1.88	96.25±2.86	96.42±2.78	0.075	.057
P100 >100	100.7±0.41	100.87±0.47	105.69±3.95	106.85±2.82	105.5±3.63	104.34±3.34	0.030	0.007
N75 ≤75	71.13±3.20	70.32±3.09	71.20±4.09	71.16±3.74	69.43±4.62	67.83±3.07	0.330	0.028
N75 >75	76.42±0.30	75.08±1.20	76.58±3.22	77.45±1.6	76.87±3.88	76.28±4.45	0.149	0.089
N145 ≤145	135.19±5.49	133.15±6.19	136.09±5.64	134.88±5.88	134.34±7.41	133.65±7.64	0.076	0.080
N145 >145	145.98±3.06	145.48±3.55	146.33±5.62	145.96±5.00	146.12±5.67	146.25±3.25	0.862	0.741
N75-P100 ≤5	4.98±0.49	4.93±0.43	4.97±0.25	4.91±0.27	4.90±0.17	4.88±0.16	0.091	0.093
N75-P100 >5	5.25±0.14	5.34±0.16	5.29±1.10	5.23±0.14	5.42±0.22	5.41±0.22	0.055	0.086

TABLE: 2 COMPARISON OF VEP RESPONSES IN GROUP IIA AND GROUP IIB PATIENTS

	Group IIA		Group IIB		P VALUE	
VEP PARAMETERS	Right eye Mean± SD	Left eye mean±SD	Right eye Mean±SD	Left eye mean±SD	(Right)	(left)
P100 ≤100	98.37±1.81	97.97±1.88	96.25±2.86	96.42±2.78	0.092	0.168
P100 >100	105.69±3.95	106.85±2.82	105.5±3.63	104.34±3.34	0.907	0.082
N75 ≤75	71.20±4.09	71.16±3.74	69.43±4.62	67.83±3.07	0.327	0.065
N75 >75	76.58±3.22	77.45±1.6	76.87±3.88	76.28±4.45	0.707	0.330
N145 ≤145	136.09±5.64	134.88±5.88	134.34±7.41	133.65±7.64	0.451	0.614
N145 >145	146.33±5.62	145.96±5.00	146.12±5.67	146.25±3.25	0.862	0.741
N75-P100 ≤5	4.97±0.25	4.91±0.27	4.90±0.17	4.88±0.16	0.614	0.08
N75-P100 >5	5.29±1.10	5.23±0.14	5.42±0.22	5.41±0.22	0.165	0.6

TABLE: 3 COMPARING VEP RESPONSES WITH HbA1C IN GROUP IIA AND GROUP IIB PATIENTS

	Group IIA				Group IIB				P value			
	HbA1c≤ 7		HbA1c>7		HbA1c≤7		HbA1c>7		HbA1c≤7		HbA1c>7	
VEP WAVE FORMS	Righteye Mean± SD	Left eye mean±SD	Right eye Mean± SD	Left eye Mean±SD	Righteye Mean± SD	Left eye mean±SD	Right eye Mean± SD	Left eye mean±SD	Righte eye	Left eye	Right eye	Left eye
P100	99.46±2.18	99.54±3.51	107.72±3.19	106.72±4.04	98.17±3.81	98.44±3.76	107.21±3.54	105.11±4.35	0.316	0.045	0.776	0.471
N75	72.98±5.17	72.42±4.41	77.47±5.12	76.34±3.15	71.83±4.99	71.69±5.22	76.07±8.39	77.11±10.82	0.576	.709	0.189	0.584
N145	137.75±9.01	139.73±10.24	139.31±6.1	136.91±5.7	137.5±11.62	134.64±9.49	138.69±7.15	136.57±8.07	0.953	0.209	0.848	0.927
N75-P100	4.94±0.43	4.91±0.46	4.87±0.3	4.91±0.31	5.13±0.33	5.17±.034	5.07±0.31	5.04±0.29	0.253	0.123	0.224	0.428

TABLE: 4 DURATION OF DIABETES AND WAVE PATTERNS OF VEP IN GROUP IIA & IIB PATIENTS

DURATION IN YEARS	Group IIA			Group IIB			P value		
	0-10	11-20	>20	0 -10	11 -20	>20	0 -10	11 - 20	>20
	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD			
P100	100.21±3.35	102.58±2.22	107.37±3.10	98.8±3.64	101.46±5.16	107.29±5.72	0.319	0.253	0.965
N75	74.15±5.38	76.78±4.62	76.76±3.93	72.36±3.42	77.14±7.51	75.5±2.45	0.315	0.053	0.901
N145	140.79±10.43	132.79±5.74	141.03±5.59	141.43±9.28	132.0±8.83	139.25±6.34	0.871	0.794	0.528
N75-P100	4.84±0.46	4.95±0.35	4.94±.035	5.14±0.40	5.08±0.22	4.87±0.13	0.085	0.071	0.661

TABLE NO: 5

HbA1c level and P 100 latency in Group II $_{A4}$ and Group II $_{A5}$

HbA1c	Right eye		Left eye	
	≤ 100ms	> 100ms	≤ 100ms	> 100ms
≤ 7.0 (12)	8	4	9	3
> 7.0 (8)	0	8	1	7
Mean	98.37 / 0	107.7/101.6	98.08/97.5	104.08/108.03
SD	1.81 / 0	3.19/0.63	1.99/0	3.26/1.69
'p' value		0.004 Significant		0.031 Significant

TABLE NO: 6

HbA1c level and N 75 latency in Group II $_{A4}$ and Group II $_{A5}$

HbA1c	Right eye		Left eye	
	≤ 75ms	> 75ms	≤ 75ms	> 75ms
≤ 7.0 (12)	8	4	9	3
> 7.0 (8)	5	3	2	6
Mean	70.53/80.95	73.0/77.87	70.94/72.13	76.86/77.75
SD	4.47/3.58	2.64/1.88	4.06/2.29	1.09/1.82
'p' value		0.456 Not Significant		0.472 Not significant

TABLE NO: 7

HbA1c level and N 145 latency in Group II $_{A4}$ and Group II $_{A5}$

HbA1c	Right eye		Left eye	
	≤ 145ms	> 145ms	≤ 145ms	> 145ms
≤ 7.0 (12)	10	2	8	4
> 7.0 (8)	7	1	7	1
Mean	134.9/137.7	152/150	134.2/135.5	150.6/146.2
SD	6.18/4.66	7.78/0	7.06/4.63	5.50/0
'p' value		0.414 Not significant		0.160 Not significant

TABLE NO: 8

HbA1c level and N75-P100 Amplitude in Group II $_{A4}$ and Group II $_{A5}$

HbA1c	Right eye		Left eye	
	≤ 5 µv	> 5 µv	≤ 5 µv	> 5 µv
≤ 7.0 (12)	6	6	6	6
> 7.0 (8)	6	2	5	3
Mean	4.59/4.74		4.53/4.70	
SD	0.27/0.23		0.32/0.18	
'p' value	0.313 Not significant		0.312 Not significant	

TABLE NO: 9

HbA1c level and P 100 latency in Group II $_{B4}$ and Group II $_{B5}$

HbA1c	Right eye		Left eye	
	≤ 100ms	> 100ms	≤ 100ms	> 100ms
≤ 7.0 (13)	9	4	8	5
> 7.0 (7)	0	7	1	6
Mean	98.44/98.01	98.17/97.1	107.21/105.60	105.11/106.01
SD	3.75/3.65	3.81/3.75	3.54/3.65	4.35/4.45
'p' value	< 0.001 Significant		0.002 Significant	

TABLE NO: 10

HbA1c level and N 75 latency in Group II $_{B4}$ and Group II $_{B5}$

HbA1c	Right eye		Left eye	
	≤ 75ms	> 75ms	≤ 75ms	> 75ms
≤ 7.0 (13)	10	3	10	3
> 7.0 (7)	4	3	4	3
Mean	71.82/70.50	73.07/72.58	71.69/75.05	74.11/75.05
SD	4.99	8.39	5.22	10.82
'p' value	0.680 Not significant		0.505 Not significant	

TABLE NO: 11

HbA1c level and N 145 latency in Group II $_{B4}$ and Group II $_{B5}$

HbA1c	Right eye		Left eye	
	≤ 145ms	> 145ms	≤ 145ms	> 145ms
≤ 7.0 (13)	10	3	11	2
> 7.0 (7)	6	1	7	0
Mean	137.50/140.5	138.64/135.5	134.63/135.5	136.57/135.65
SD	11.62	7.15	9.49	8.07
'p' value	0.816 Not significant		0.653 Not significant	

TABLE NO: 12

HbA1c level and N75-P100Amplitude in Group II $_{B4}$ and Group II $_{B5}$

HbA1c	Right eye		Left eye	
	≤ 5 µv	> 5 µv	≤ 5 µv	> 5 µv
≤ 7.0 (13)	8	5	6	7
> 7.0 (7)	4	3	5	2
Mean	5.13/4.90	5.07/5.12	5.17/4.85	5.04/4.95
SD	0.33	0.31	0.34	0.29
'p' value	0.711 Not significant		0.402 Not significant	

Fig: 1

P100,N75,N145 LATENCIES & N75-P100 AMPLITUDE IN GROUPI,II A & II B PATIENTS(RIGHT EYE)

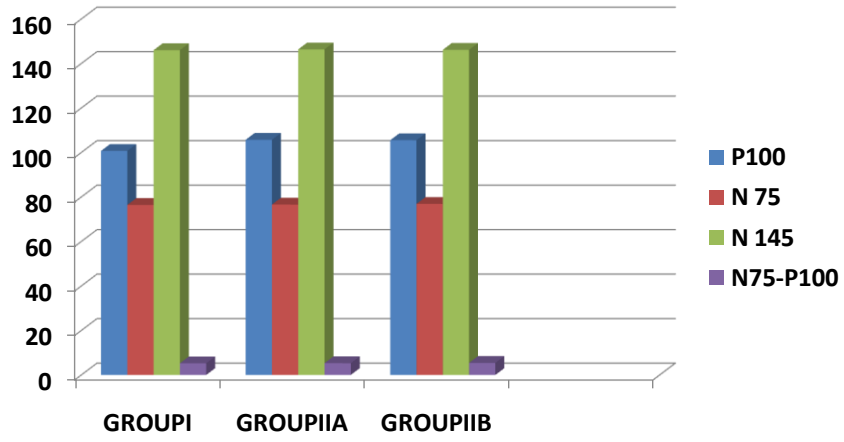


Fig: 2

P100,N75,N145 LATENCIES & N75-P100 AMPLITUDE IN GROUPI,IIA & II B PATIENTS(LEFT EYE)

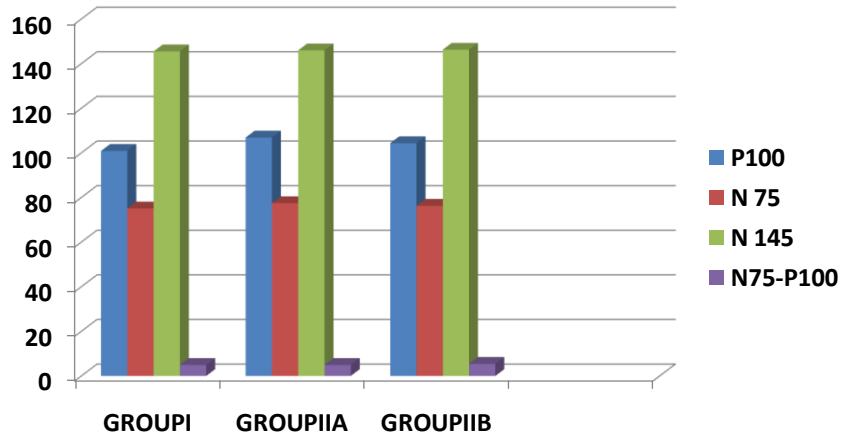


Fig - 3

P100,N75,N145 LATENCIES & N75-P100 AMPLITUDE IN GROUP II A & IIB PATIENTS(RIGHT EYE)

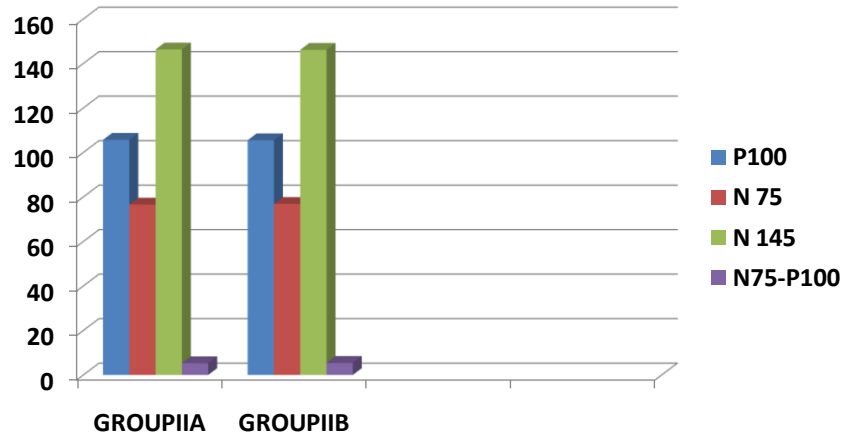


Fig:4

P100,N75,N145 LATENCIES & N75-P100 AMPLITUDE IN GROUP IIA &IIB PATIENTS(LEFT EYE)

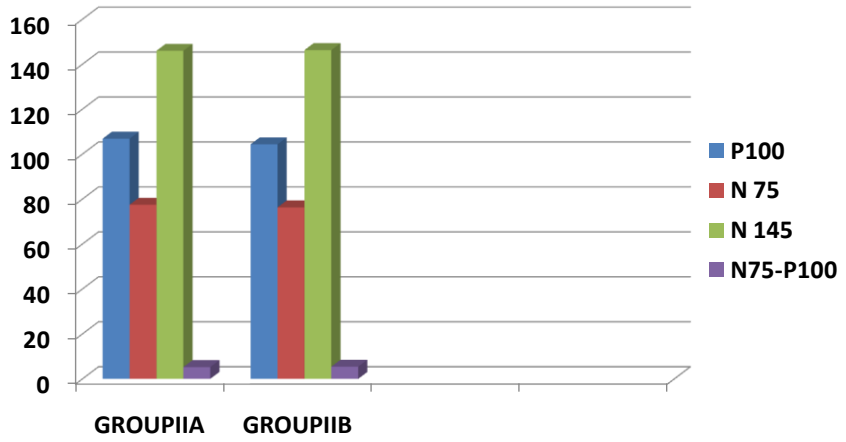


Fig: 5

COMPARING VEP RESPONSES WITH HbA1C>7IN GROUPIIA & IIB(RIGHT EYE)

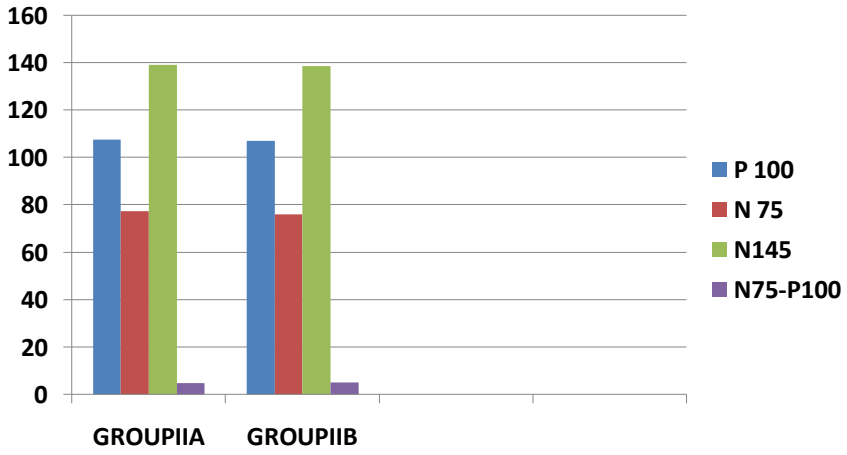


Fig: 6

COMPARING VEP RESPONSES WITH HbA1C > 7 IN GROUP II A & II B (LEFTEYE)

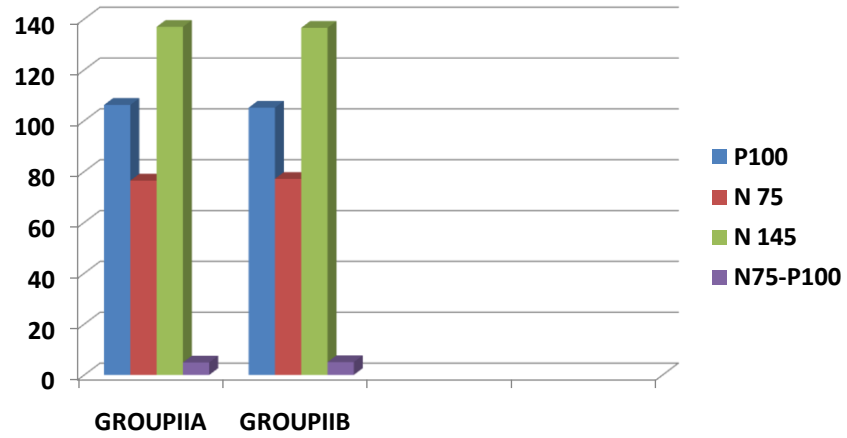


Fig -7

COMPARING VEP RESPONSES WITH HbA1C < 7 IN GROUP II A & II B (RIGHTEYE)

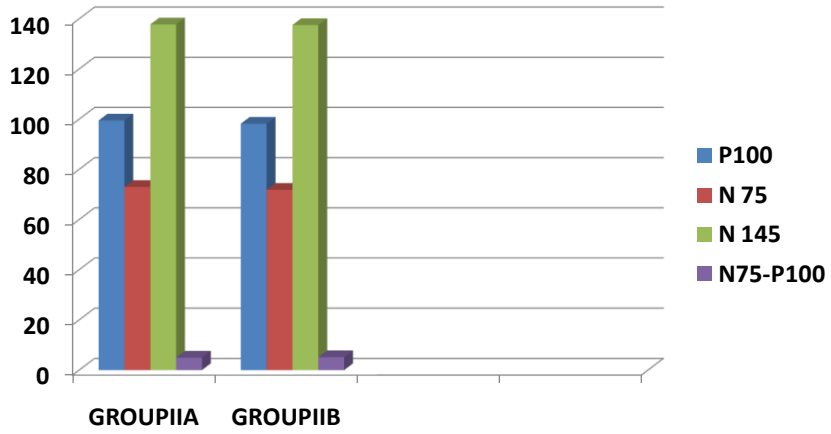


Fig: 8

COMPARING VEP RESPONSES WITH HbA1C < 7 IN GROUP II A & II B (LEFTEYE)

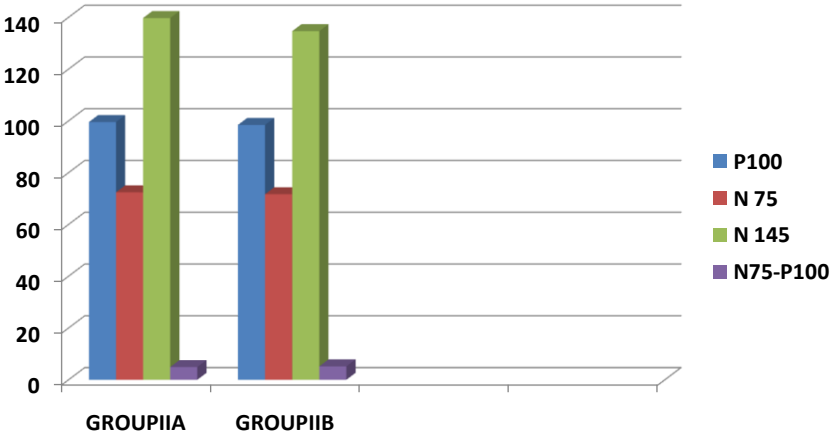


Fig :9-HbA1c level and P100 latency in Group II $_A$ patients

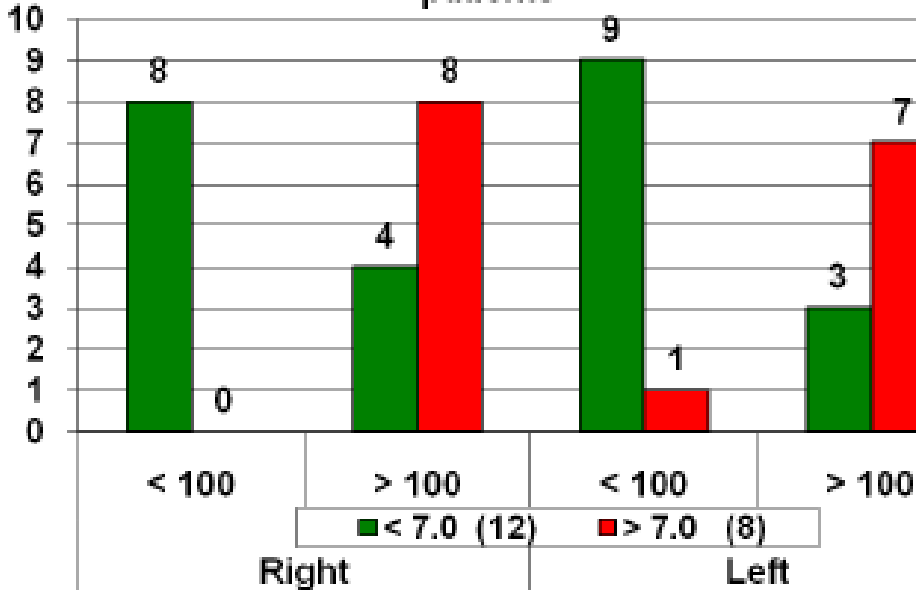


Fig:10-HbA1c level and N 75 latency in Group II $_A$ patients

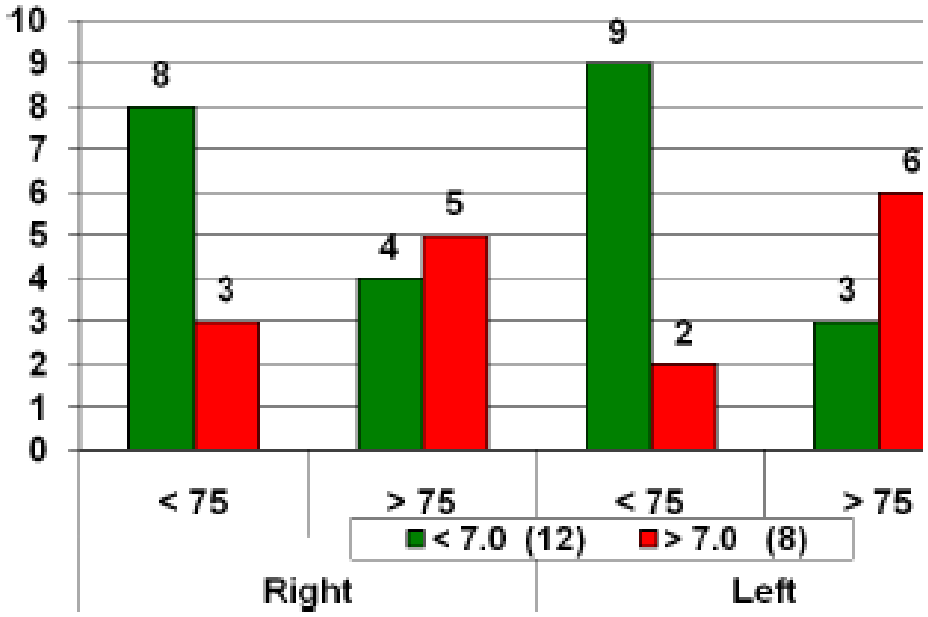


Fig:11-HbA1c level and N 145 latency in Group II $_A$ patients

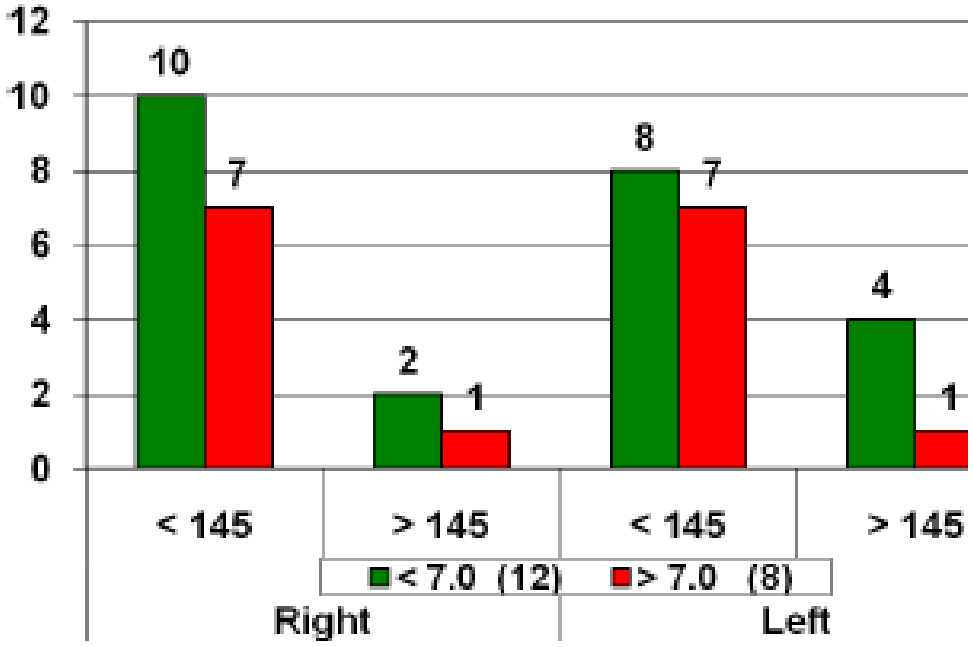


Fig:12- HbA1c level andN75-P100 amplitude in Group II $_A$ patients

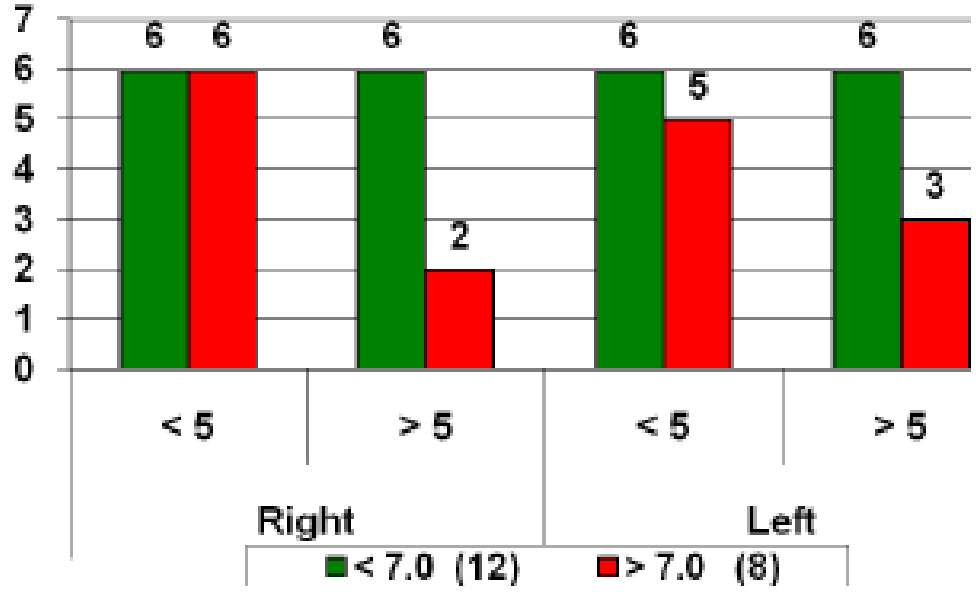


Fig:13-HbA1c level and P100 latency in Group II $_B$ patients

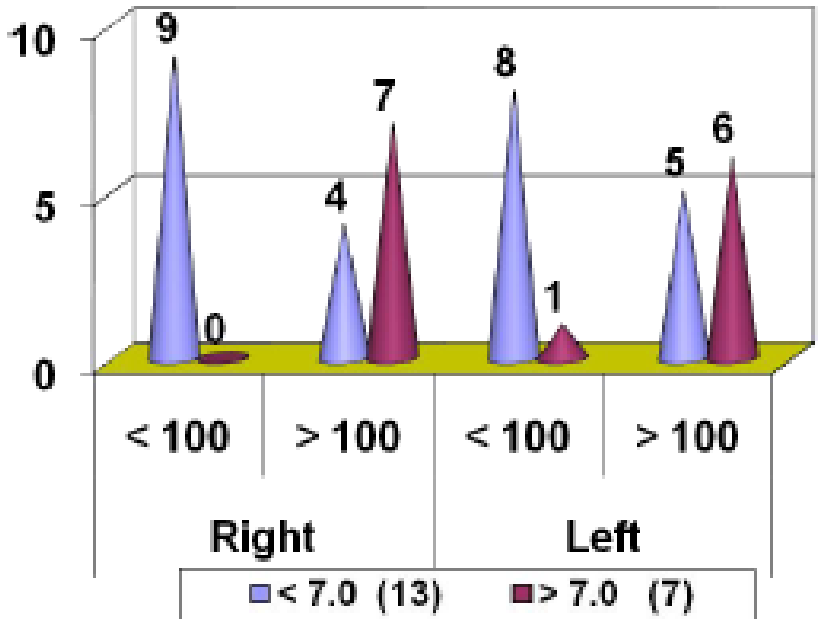


Fig 14-HbA1c level and N75 latency in Group II $_B$ patients

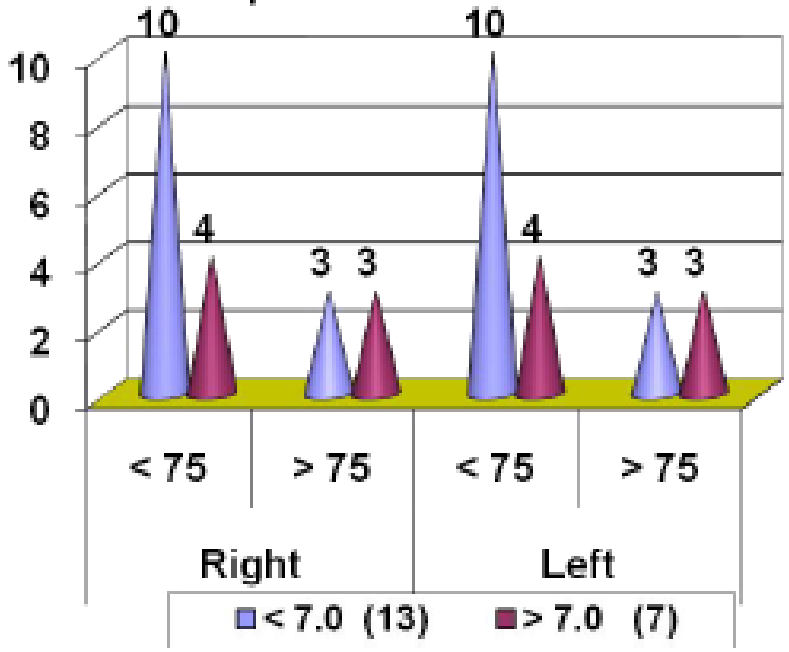


Fig-15- HbA1c level and N145 latency in Group II $_B$ patients

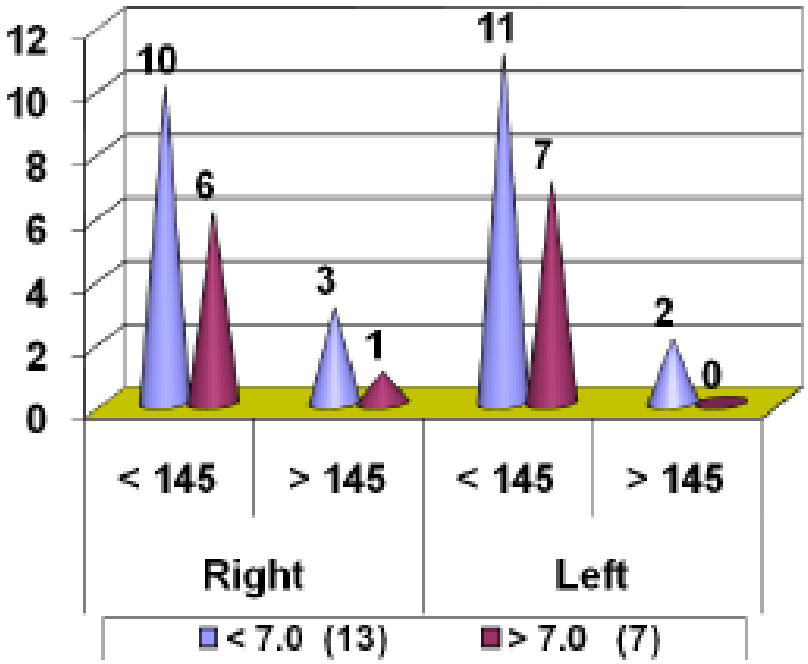


Fig16- HbA1c level and N75-P100 amplitude in Group II $_B$ patients

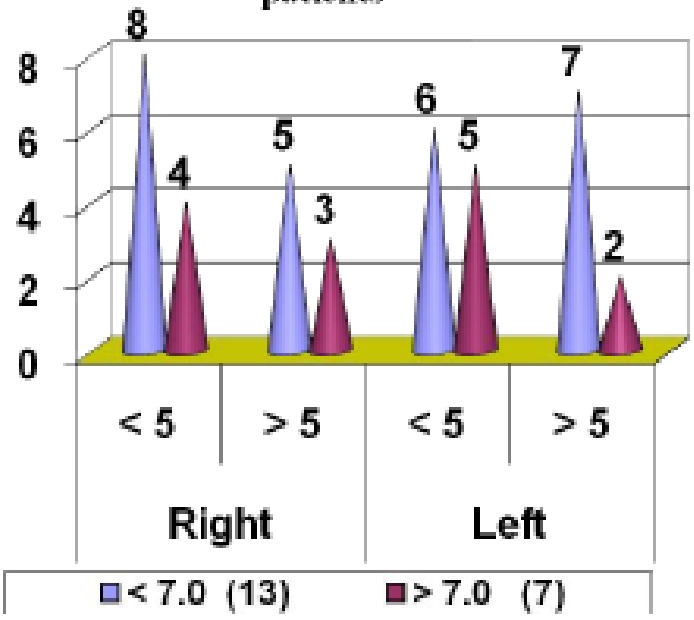


Fig: 17
DURATION Of DIABETES & VEP RESPONSES IN GROUP II A PATIENTS

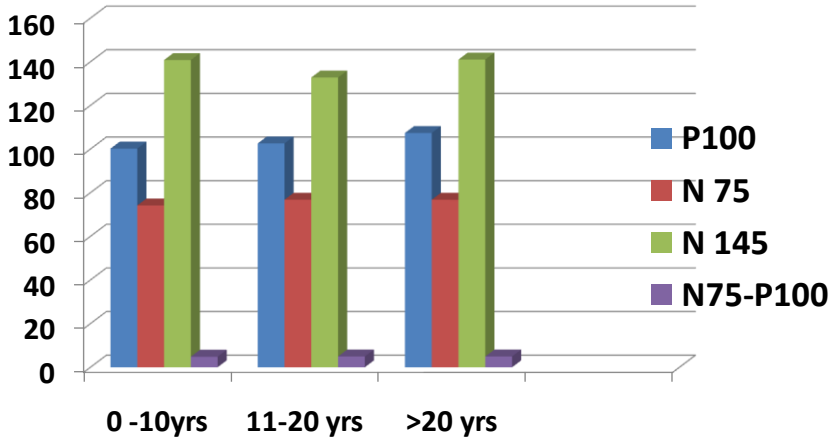


Fig: 18
DURATION Of DIABETES & VEP RESPONSES IN GROUP II BPATIENTS

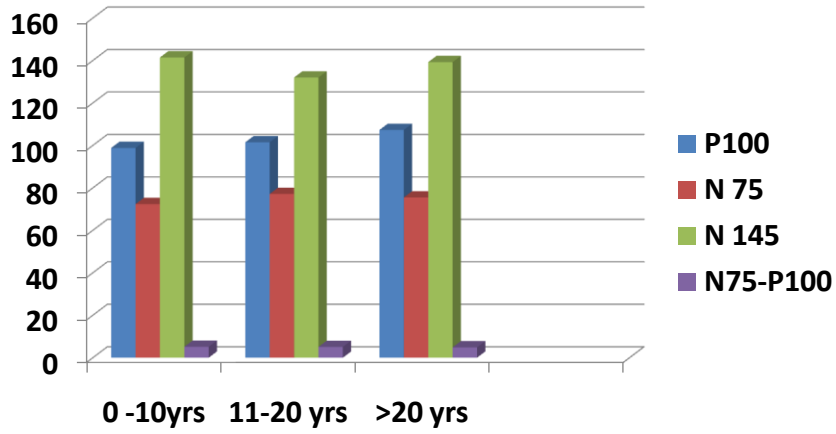


Fig: 19
VEP RESPONSES & 0- 10 YRS OF DURATION IN GROUP II A & IIB PATIENTS

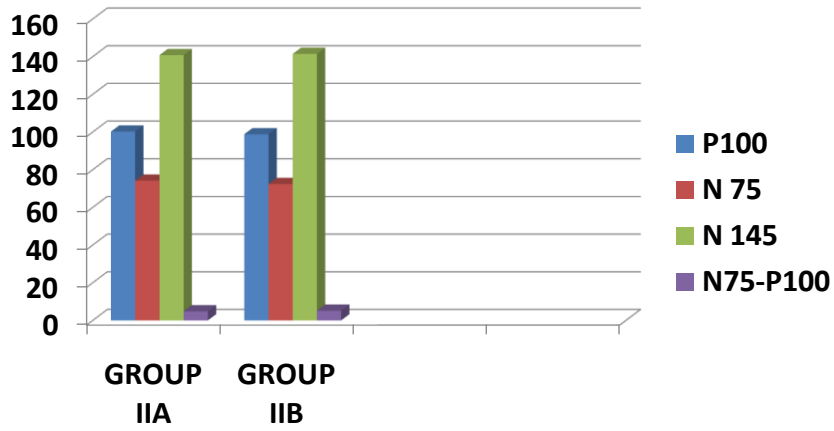


Fig: 20
VEP RESPONSES & 11 -20 YRS OF DURATION IN GROUP II A & IIB PATIENTS

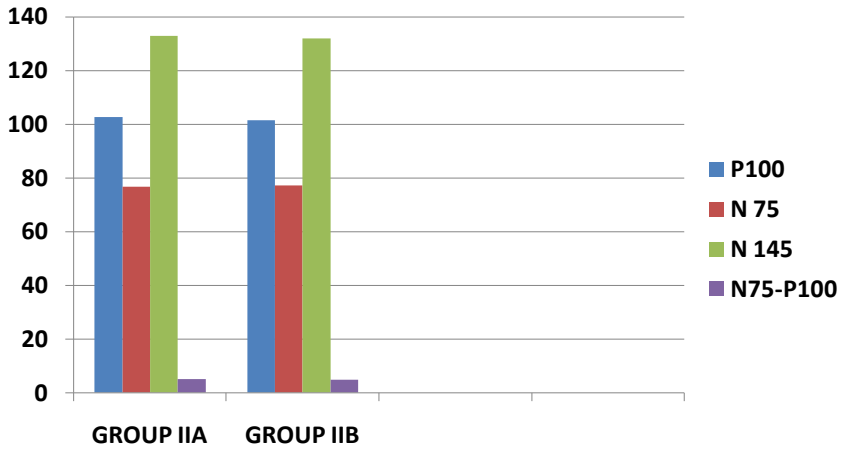
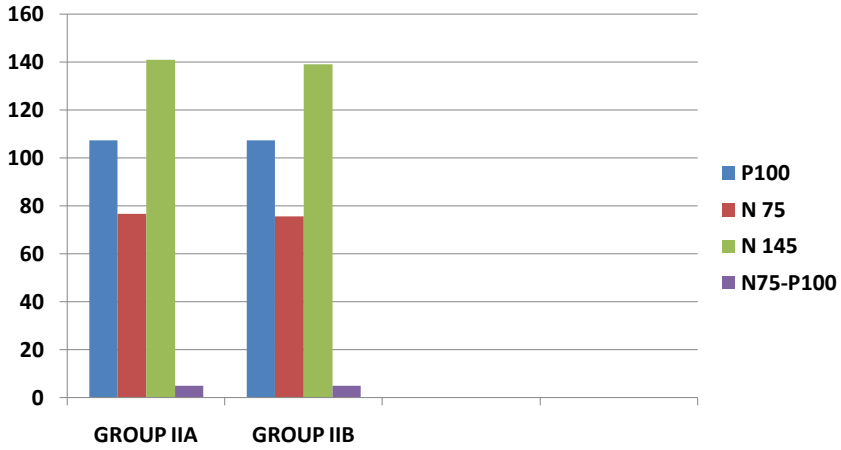


Fig: 21

COMPARISON OF VEP RESPONSES WITH > 20 YRS OF DURATION BETWEEN GROUP II A & IIB PATIENTS



DISCUSSION

DISCUSSION

The present study was done on 40 diabetics and 40 controls in the age group of 30-70 years. The P100 latencies of VEP were significantly delayed in Group II_A and Group II_B patients as compared to Group I subjects. This finding was consistent with the observations of Varkonyi T et al [25], Dolu H et al [14], Azal O et al [42], Szabela D et al [43], Li P et al [44], Fierro B et al [12], Parisi V et al[13], Karlika D et al[15], Verotti A et al [24], Micheal Algan et al [26], and Ziegler O et al [27] who reported similar changes in their study.The significant correlation of the delay in the P100 latency with increased duration of diabetes , corroborated with the findings of Dolu H et al [14], Azal O et al [42] and Li p et al [44]. A positive correlation was documented between glycemic control and prolonged P100 latencies. This findings was consistent with the observations of Sami ulus [17], Pozzessere et al [18]. The N75 and N145 latencies were not significantly delayed in Group II_A and Group II_B patients as compared to Group I subjects.VEP responses were compared between Group II_A and Group II_B patients. No significant difference was found between these two groups. This finding was consistent with the observations of Pozzessere G et al [18]. Comparison of VEP responses was done between Group II_A and Group II_B in relation to glycemic control and duration of disease.

No significant difference was found between these two groups. This findings was consistent with the observations of Algan M et al [26].

The P100 wave form is generated in striate and peri striate occipital cortex due to activation of primary visual cortex and also due to the discharge of thalamo cortical fibres. N75 reflects the activity of fovea and primary visual cortex, while N145 reflects the activity of the visual association area. The P100 is a prominent peak that shows relatively little variation between the subjects, minimal with in subject's interocular difference, and minimal variation with repeated measurements overtime. Our findings signify that there is a definite neurological deficit in diabetes mellitus. The exact pathophysiology of optic neuropathy is not clear, but it seems to be multifactorial involving metabolic and vascular factors. The possible mechanisms for the development of optic nerve dysfunction are

1) Polyol pathway.
2) Vessel ischaemia.

Polyol pathway: The polyol pathway refers to the intra cellular mechanisms responsible for changing the number of hydroxyl units on a glucose molecule. In the sorbitol pathway, glucose is first transformed to sorbitol and then to fructose.

This process is activated by the enzyme aldose reductase. Although glucose is converted readily to sorbitol, the rate at which sorbitol can be converted to fructose and then metabolized is limited. Sorbitol is an osmotically active, and it has been hypothesized that the presence of excess intra cellular amounts may alter the cell function in nerves and blood vessels. Increased sorbitol is also associated with a decrease in myoinositol and reduced ATPase activity in axons. The reduction of these compounds may contribute to the pathogenesis of optic nerve fibre loss.

Vessel ischaemia:

Thickening of the walls of nutrient vessels that supply the nerve leads to vessel ischaemia may contribute to the development of segmental demyelination. This process is accompanied by a slowing of nerve conduction.

Neuropoietic cytokines including interleukin-1(IL-1), IL-6, leukemia inhibitory factor (LIF), ciliary neuro-trophic factor(CNTF), tumour necrosis factor alpha(TNF-alpha), and transforming growth factor beta(TGF-beta), exibit pleiotrophic effects on the homeosatsis of the glia and on the neurons in the central, peripheral and the autonomic nervous systems. These cytokines are produced locally by the resident and infiltrating macrophages, lymphocytes, mast cells, fibroblasts and sensory neurons. The accumulation of these mediators

probably delays the conduction in the visual pathway, which could be the probable cause of the delay in the P100 latency which was found in the Group II_A and II_B as compared to the Group I subjects. With the increase in duration of diabetes, the accumulation of these mediators also increases, which can cause further delay in the latencies in diabetics with more duration of disease as compared to diabetics with a lesser duration of the disease.

The delayed P100 latencies which were recorded in the absence of retinopathy are indicative of anterior visual pathway affection in diabetics and it is an expression of structural damage at the level of myelinated optic nerve fibres. P100 latencies were observed to be more prolonged in those who had poor glycemic control as a result of more prolonged exposure to toxic metabolites.

The progressive increase in P100 latency values are a direct sign of retinal ganglion cell damage, which takes place even before the first ophthalmoscopically detectable signs of diabetic retinopathy arise.

Therefore VEP should be considered as a valid method for detecting prediabetic retinopathy, which could contribute greatly to the prevention of diabetic retinopathy and its complications.

SUMMARY

&

CONCLUSION

SUMMARY

- The visual evoked responses was studied in both type1 and type 2 diabetic patients as well as in normal subjects.
- The P100 latency was significantly delayed in both type 1 and type 2 diabetic patients as compared to the normal subjects.
- A positive correlation was documented between prolonged P100 latencies and increased duration of diabetes.
- The P100 latency was significantly delayed in those patients who had poor long term glycemic control .
- The delay in N75, N145 latencies and decrease in N75-P100 amplitude values were not statistically significant in diabetics as compared to control subjects.
- VEP responses were compared between type1 and type 2 diabetes.There was no statistically significant difference observed between these two groups.
- VEP responses were compared between type1 and type 2 diabetes in relation to glycemic control & duration of disease. No statistically significant difference was observed between these two groups.

CONCLUSION

The delay in P_{100} latency was observed in diabetic patients before the development of overt retinopathy. The possible mechanisms for the development of optic nerve dysfunction which could lead on to delay in P_{100} latencies could be due to

- Increased intracellular sorbitol level
- Reduced myoinositol and ATPase activity
- Vessel ischemia
- Accumulation of IL-1,IL-6,Leukemia inhibitory factor, ciliary neuro-tropic factor (CNTF), tumour necrosis factor alpha and transforming growth factor beta
- Structural damage at the level of myelinated optic nerve fibres
- Retinal ganglion cell damage

So, VEP measurement which is a highly sensitive, reliable, non invasive and reproducible method for detecting the early alterations in the central optic pathways in diabetics. It should be recommended whenever possible and this must be added to the list of screening tools for a more complete and early assessment of neurological involvement of the diabetic patients to advise them for an early and proper management of the disease.

GLYCEMIC CONTROL :

The Diabetes Control and Complications Trial (DCCT) provided definitive proof that reduction in chronic hyperglycemia can prevent many of the early complications of DM. The DCCT demonstrated that improvement of glycemic control reduced nonproliferative and proliferative retinopathy (47% reduction). Improved glycemic control also slowed the progression of early diabetic complications. The benefits of an improvement in glycemic control occurred over the entire range of HbA_{1C} values, suggesting that at any HbA_{1C} level, an improvement in glycemic control is beneficial. The goal of therapy is to achieve an HbA_{1C} level as close to normal as possible, without subjecting the patient to excessive risk of hypoglycemia.

The most effective therapy for diabetic retinopathy is prevention. Intensive glycemic control will delay the development or slow the progression of retinopathy in individuals with either type 1 or type 2 DM. Regular, comprehensive eye examinations are essential for all individuals with DM. Most diabetic eye disease can be successfully treated if detected early.

LIMITATIONS OF THE STUDY:

The present study was a basic screening of diabetic individuals for optic nerve dysfunction. A larger sample size and a longitudinal study will be of great value to demonstrate whether a good glycemic control would reverse the structural abnormalities of the optic nerve.

FUTURE SCOPE OF THE PRESENT STUDY:

The current study is of public health importance as it suggests that by screening for and detecting optic neuropathy, physician can advice patients regarding glycemic control of diabetes and prevention of retinopathy.

This study can be further extended to involve a larger sample from a group of population.

Further studies are needed to determine whether a good glycemic control would reverse the structural abnormalities of the optic nerve or prevent the early progression of diabetic retinopathy.

Further studies are essential to determine whether short-term strict control of blood glucose can improve abnormal visual evoked potentials (VEPs) in poorly controlled diabetic patients with no overt diabetic complications.

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ANNEXURES

CONSENT FORM

Dr.S.Navurang, Post graduate student in the Department of Physiology, Coimbatore Medical College, Coimbatore is studying the visual evoked potentials in diabetes mellitus. The procedure of recording of visual evoked potential, collection of blood specimen for HbA_1C were explained to me clearly. I understand that there are no risks involved in the above procedure. I hereby give my consent to participate in this study. The data obtained herein may be used for research and publication.

Signature :

Name :

Place :

VISUAL EVOKED POTENTIALS IN DIABETES MELLITUS

NAME:

AGE:

SEX:

OCCUPATION:

ADDRESS:

PRESENT HISTORY:

HISTORY OF DIABETES: YES/ NO

DURATION OF DIABETES:

PAST HISTORY:

HISTORY OF HYPERTENSION: YES/ NO

HISTORY OF CORONARY ARTERY DISEASE: YES/ NO

HISTORY OF GLAUCOMA AND CATARACT: YES/ NO

FAMILY HISTORY:

FAMILY HISTORY OF DIABETES/ HYPERTENSION: YES/ NO

VITAL SIGNS:

BLOOD PRESSURE :

PULSE RATE:

RESPIRATORY RATE:

CLINICAL EXAMINATION :

CVS:

RS:

ABDOMEN:

CNS:

OCULAR EXAMINATION:

CATARACT : PRESENT/ ABSENT

INTRA OCULAR TENSION: NORMAL / INCREASED

INVESTIGATIONS:

FASTING BLOOD SUGAR:

POSTPRANDIAL BLOOD SUGAR:

HbA_1C LEVEL:

VISUAL EVOKED RESPONSE:

P_{100} LATENCY: NORMAL/ DELAYED

N_{75} LATENCY: NORMAL/ DELAYED

N_{145} LATENCY: NORMAL/ DELAYED

N75-P100 AMPLITUDE: NORMAL/ DECREASED

Master chart -Group II $_A$: Visual evoked responses in Type I Diabetes mellitus

S.NO	Age	Blood sugar		HbA1C	Duration	Right eye				Left eye			
		FBS (mg/dl)	PPBS (mg/dl)			N75 (msec)	P100 (msec)	N145 (msec)	N75-P100µv	N75 (msec)	P100 (msec)	N145 (msec)	N75-P100µv
1	50	130	209	7.9	25	75	106.5	138.5	4.58	76.25	107.5		4.64
2	45	113	143	6.5	16	75	100	132.5	5.2	74.5	96.5	130.5	5.4
3	52	178	278	8.2	21	74	112	150	5	76	108	139.5	5.2
4	46	99	165	6	17	73.5	98.5	135	5.2	75.6	98.75	130	5.4
5	55	78	207	8.1	24	85	112.5	143.75	4.84	77.5	110	146.25	4.72
6	42	129	198	7.1	12	78.5	103.75	130	5	73.75	97.5	128.5	5
7	33	112	142	6.5	8	66.5	95	125	5.4	65	95	127.5	5.2
8	52	268	179	6.8	23	73.75	102.5	133.75	5.48	75	107.5	148.75	5.32
9	53	128	210	6.2	9	78.5	100	143.75	5.24	70	98.5	142.75	5.14
10	51	140	216	7.5	23	76.25	105.5	138.5	4.58	80	108.75	138.5	4.64
11	56	401	260	6.9	6	77.5	100	157.5	4.21	77.5	101	158.75	4.32
12	58	249	390	7.5	21	81.5	108.5	142.5	5.2	80	110	140.5	5.2
13	32	130	218	6.1	14	68.5	96.5	132.5	5	71.5	95	128.5	5
14	42	105	218	6.5	26	80	101.5	146.5	4.8	77.5	103.75	146.5	4.28
15	47	197	283	6.4	18	70	98.5	127.5	4.53	73.5	100	130	4.88
16	48	88	217	6.9	3	75.5	101	140	5.34	75	99.5	148.5	5.28
17	50	190	315	7.5	21	70	108	134.75	5.28	70.5	105.5	130.75	5.33
18	40	128	216	6.4	15	62.5	98.5	143.5	4.48	64.5	99.5	145	4.32
19	55	390	249	7.8	8	83.5	105	136.5	4.48	76.75	106.5	133.75	4.52
20	38	130	218	6.7	8	74.5	101.5	135.5	4.53	69.5	107.5	137.5	4.64

Master chart -Group II $_B$: Visual evoked responses in Type II Diabetes mellitus

S.NO	Age	Blood sugar		HbA1C	Duration	Right eye				Left eye			
		FBS (mg/dl)	PPBS (mg/dl)			N75 (msec)	P100 (msec)	N145 (msec)	N75-P100µv	N75 (msec)	P100 (msec)	N145 (msec)	N75-P100µv
1	65	317	459	7.8	12	78.5	107.5	140	5.65	87.5	102.5	142.5	5.65
2	42	175	263	6	8	67.5	97.5	138.5	4.46	71.5	101.5	138.5	4.48
3	43	132	188	6.2	6	77.5	102.5	138.75	5	77.5	100	135	5.2
4	57	140	176	6.8	13	76.25	93.75	127.5	5.42	76.25	95	127.5	5.42
5	50	204	306	7	11	78.5	102.5	125.5	5.4	81.5	101.5	122.5	5.4
6	48	241	339	7.5	22	62.5	105.5	135.5	5	62.5	98.5	128.5	5
7	42	167	315	7.4	14	76	105	130	5.2	82.5	102.5	123.75	5
8	58	162	287	7	7	72.5	102.5	123.75	5	72.5	102.5	123.75	5
9	50	208	367	8.1	25	67.5	106.25	145	4.68	67.5	106.5	145	4.78
10	67	150	221	6.5	18	72.5	95	130	5	67.5	93	127.5	5
11	66	210	335	8.1	6	86.5	105	148.5	5.17	86.25	107.5	133.75	5.12
12	47	130	307	6.9	21	75	100	160	5.8	70	101.5	150	5.8
13	55	124	194	6.8	9	72.5	102.5	152.5	5.38	71.5	103.5	150.5	5.38
14	59	152	296	7	17	66.5	93.75	122.5	5	66.25	92.5	122.5	5
15	48	131	212	6.9	8	72.5	100	141.5	5.31	65	97.5	140	5.21
16	65	402	465	8.2	6	65.5	115	141.5	4.9	67.5	112	140	4.9
17	46	159	313	6.5	14	72.5	92.5	135	5	70	95	140	5
18	37	231	198	7.9	13	75	106.25	130	4.9	65	106.25	142.5	4.8
19	47	109	280	6.5	22	70	98.75	147.5	5	77.5	100	136.25	5.48
20	58	235	180	7	7	60	95	144.5	4.9	65	96.25	136.25	4.8

Master chart –Group I : Visual evoked responses in control subjects

S.NO	Age	Blood sugar		Right eye				Left eye			
		FBS (mg/dl)	PPBS (mg/dl)	N75 (msec)	P100 (msec)	N145 (msec)	N75-P100µv	N75 (msec)	P100 (msec)	N145 (msec)	N75-P100µv
1	50	87	122	72.5	97.5	126.25	5.2	71.5	98.5	127.75	5.4
2	45	89	145	73.75	100	126.25	5.2	73.75	98.75	126.25	5
3	52	92	160	75	100	140.5	5.47	73.5	101.5	138.5	5.5
4	46	100	167	76.25	98.75	140.5	5	75	98	138.5	5
5	55	98	154	72.5	97.5	140.5	5	76.25	98.75	145	4.8
6	42	78	160	73.75	97.5	140.5	5	76.5	98.75	131	5.2
7	33	89	145	75	95.5	125	5.10	66.5	97.5	140.5	5.48
8	52	99	156	76.25	100.25	145	5.28	76.25	97.5	141.5	5.25
9	53	90	145	76.5	98.75	132.5	5	73.75	97.5	132	5
10	60	78	130	66.25	90	137.5	5	67.5	91	120	5
11	56	86	139	76.25	97.5	137.5	5.2	65	98.75	137	5.4
12	58	98	156	73.75	95.5	132.5	5	63.75	97.5	145	5.4
13	32	90	165	67.5	100	140	5	76.25	98.75	133.75	5.2
14	42	95	170	65	97.5	135	5.4	73.75	96.25	132.5	5
15	47	95	175	63.75	97.5	131.25	5.2	67.5	98.75	127.5	5.4
16	48	91	178	76.25	95	131.25	5.4	72.5	97.5	145	5.3
17	50	91	165	73.75	97.5	141.25	5.24	75	97.75	120	5.28
18	40	97	178	67.5	97.5	123.5	5.2	78.75	100	125.5	5.4
19	55	96	177	73.75	101.25	123.75	5	78.5	98.75	137.5	5
20	38	80	156	73.75	98	137.5	5.1	71.25	97	141	5.2

Master chart –Group I :Visual evoked responses in control subjects

S.NO	Age	Blood sugar		Right eye				Left eye			
		FBS (mg/dl)	PPBS (mg/dl)	N75 (msec)	P100 (msec)	N145 (msec)	N75-P100µv	N75 (msec)	P100 (msec)	N145 (msec)	N75-P100µv
21	35	89	139	70	99.5	137.5	5.5	70	99.5	128.5	5.3
22	40	86	156	67	98	138.5	5	67	98	130	4.2
23	55	98	165	75	97	139	5.1	75	97	128.5	4.12
24	50	90	170	71	98.5	140	5.1	71	98.5	131.5	4.6
25	40	95	175	70	96	139.5	4.1	70	96	129	4.12
26	38	95	178	65	100	140	4	65	100	129.75	4.18
27	60	91	165	69	101	138	4.1	69	101	138	4
28	58	91	178	71	100.5	137.5	3.9	71	100.5	135.5	4.5
29	52	97	177	71	99	139.5	3.8	71	99	138.5	4
30	53	96	156	71	99.5	131.75	4	71	99.5	135	4.7
31	43	86	122	72.5	98	131.5	4.2	72.5	98	128	4.7
32	54	98	145	74	98.5	138	4.1	74	98.5	136	3.8
33	42	90	160	70.5	97.5	137	4.28	70.5	97.5	130.5	3.9
34	57	95	167	68.5	98.5	136.5	4.2	68.5	98.75	128.5	3.92
35	39	95	154	69.5	98.75	135.5	3.9	69.5	98.75	131.5	4.8
36	50	91	160	67	100	137	3.8	67	100	131.5	4.4
37	48	91	145	71	100.5	137	3.9	71	100.5	138.5	3.9
38	40	97	156	69	99.5	130	3.92	69	99.5	131.5	4.12
39	38	96	145	72	99.75	130.5	4.12	72	99.75	129.5	4.12
40	53	80	130	66.5	97	125.5	4.21	66.5	97	130.5	4.2